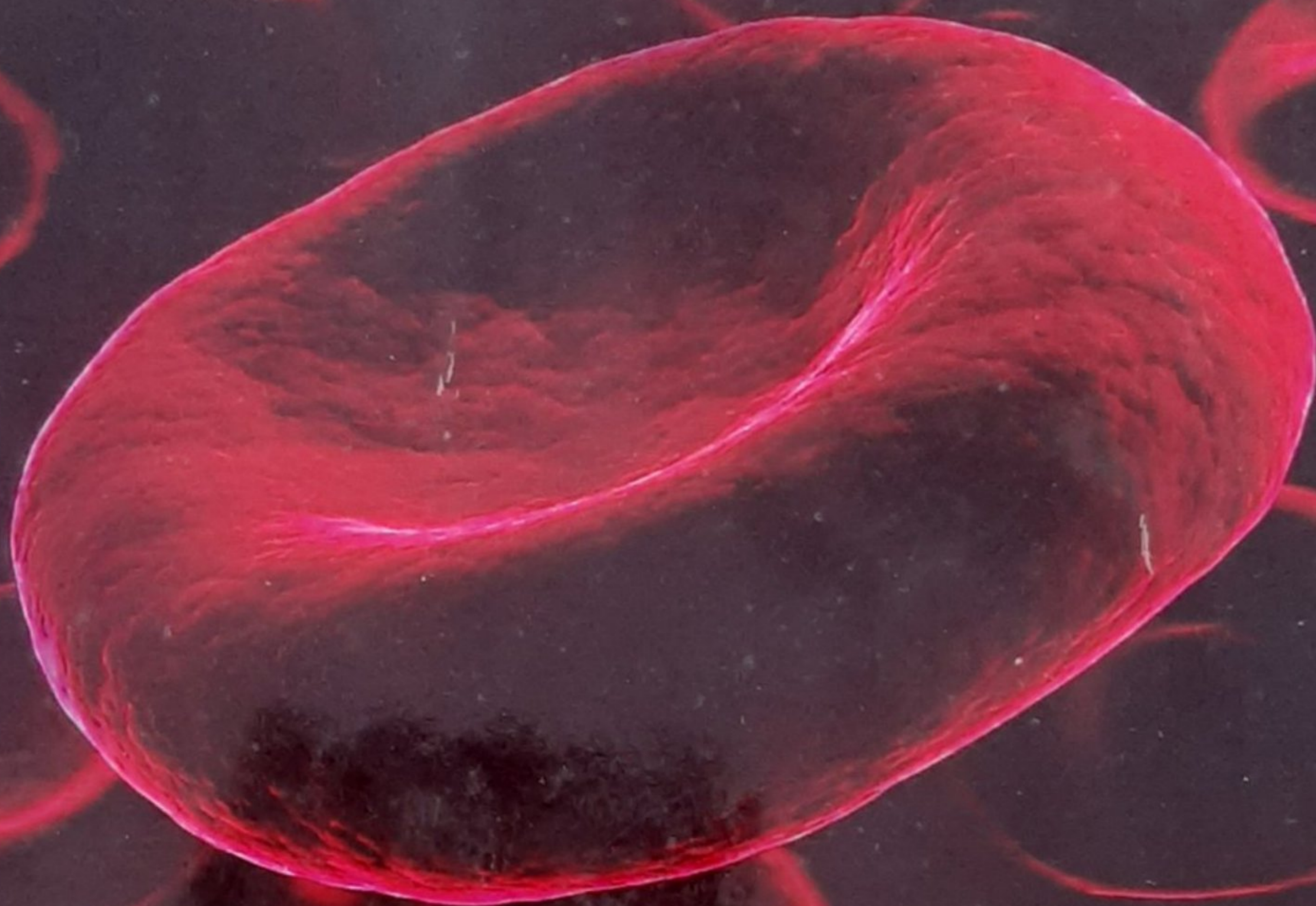


MOST UPDATED

HAEMATOLOGY

NEW EDITION



ALLAM'S

**INTERNAL MEDICINE
SERIES**



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Hematopoiesis "read only"

Erythropoiesis

Erythropoietin (EPO): produced in the kidney ^{85% and activated in liver} and liver ^{15%} in response to low oxygen levels.

1. Pluripotent hematopoietic stem cell
2. Pro-normoblast
3. Polychromatophilic normoblast (intermediate normoblast)
4. Basophilic normoblast (early normoblast)
5. Reticulocyte
6. Erythrocyte (mature red blood cell)
7. Multipotent stem cell
8. Orthochromatic "late" normoblast
9. Unipotent stem cell

Phagocytopenia

Colony-stimulating factors (G-CSF and M-CSF) + Interleukin (1L-3).

1. Pluripotent stem cell.
2. The colony forming unit Granulocyte macrophage (CFU-GM)
3. Granulocyte and monocyte progenitors (CFU-G and CFU-M)
4. Mature granulocytes + \-monocytes

Megakaryocytopoiesis "Thrombopoietin"

1. Megakaryocyte progenitors
2. Megakaryoblasts
3. Progressive maturation into platelet shedding
4. Megakaryocyte

5. Platelets

Monocytes

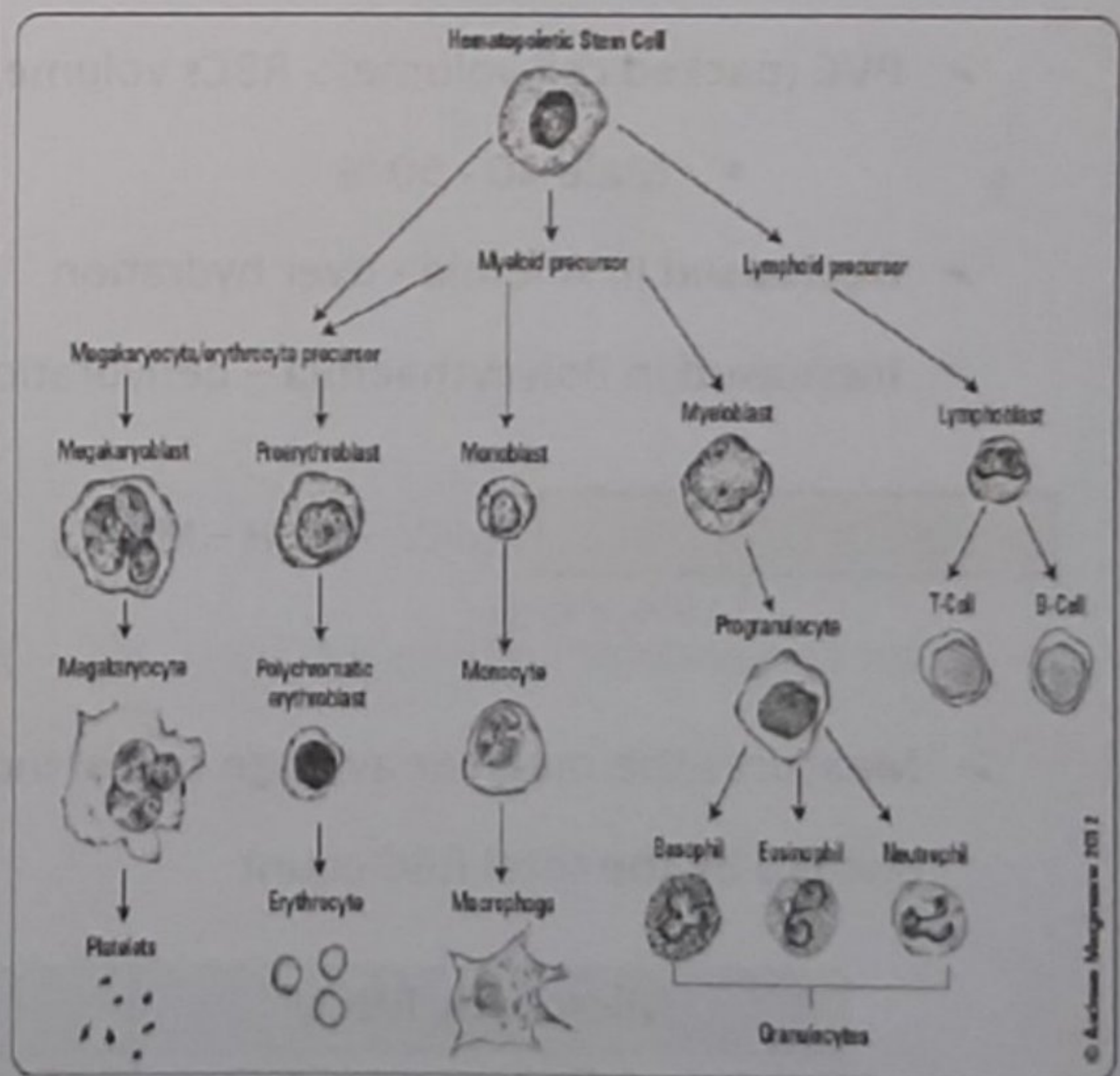
leave the circulation and differentiate further to become **fixed tissue macrophages**.

(e.g. alveolar macrophages and hepatic Kupffer cells, dermal Langerhans cells, osteoclasts, peritoneal macrophages, pleural macrophages and possibly brain microglial cells).

The granulocytes

Compartment itself is more complex Than either the **erythroid** or **megakaryocyte** compartments.

- The circulating half life of the newly rapidly deployed granulocyte is only 5-6 hr



$\begin{matrix} \text{RBC} \\ \text{Hb} \\ \text{PCV} \end{matrix} = \text{anemia}$
 $\begin{matrix} \text{cyte} \\ \text{chromic} \end{matrix} \text{ MCV} = \text{Type of anemia}$

Introduction to main parameters

1. CBC
2. RBCs indices & RDW
3. Reticulocyte
4. Peripheral blood film
5. BM examination
6. WBCs
7. Platelets
8. ESR
9. Special tests

1- CBC (Complete blood count) (RBCs – Hb – Haematocrit - WBCs + DLC – Platelets)

1- RBCs:

- Male 4.5 - 6.5 million cells/mm³
- female 3.8-5.8 million cells/mm³

2- HAEMOGLOBIN:

- Male 13-18 gm/dl
- female 12-16 gm/dl
- Average 14 gm %
- Hb % : (= patient Hb/average Hb)

Colour index

- ✓ $\text{Hb\%} / \text{RBCs\%} = 1$ (normally)
- ✓ > 1.1 hyperchromic (wrong term)
- ✓ < 0.9 = hypochromic

3- HAEMATOCRIT (HCT) :

- PVC (packed cell volume):- RBCs volume/total B volume = 1
 - Male 40 - 50 %
 - female 36-44%
- Decreased in Anemia - over hydration
- Increased in Polycythaemia – dehydration

2- RBCs Indices : (MCV – MCH – MCHC)

A- Mean corpuscular volume (MCV):- متوسط حجم الخلايا $80 - 96 \text{ fL}$ $\text{Litter} = \frac{\text{PCV} \cdot \text{HCT}}{\text{RBCs}}$

- Measures the mean or average size of individual red blood cells = the hematocrit is divided by the total RBC count

Microcytic RBCs	Macrocytic RBCs
• Iron deficiency anemia • Thalassemia. • Sideroblastic anaemia • Lead toxicity	• <u>Megaloblastic</u> :- B12 & folic acid def. • <u>Non Megaloblastic</u> : hypothyroidism , Hepatic Failure & alcoholism

B- Mean corpuscular haemoglobin (MCH):- 27-32

- Measures the amount of haemoglobin present in one RBC. = dividing the haemoglobin by the total RBCs.

C- Mean corpuscular haemoglobin concentration (MCHC):- 32-36 gm/dL

- Measures the amount of haemoglobin present in each RBC proportionate to the RBC size.

NB : The MCH (for lesser extend) and the MCHC are used to assess whether red blood cells are normochromic, hypochromic or hyperchromic.

D- Red cell distribution width (RDW): Adults: - 11.7%-14.2%

- A calculation of the variation in the size of RBCs.
- In some Anaemias, such as Megaloblastic anaemia, the amount of variation (Anisocytosis) in RBC size (along with variation in shape - poikilocytosis) causes an increase in the RDW.

3) Reticulocyte (Adults: - 0.2%-2.2%)

- **Value :** Reflects Bone Marrow activates.
- It is increased in
 - ✓ Haemolytic anaemia.
 - ✓ Haemorrhage.
 - ✓ Hypersplenism.
- It is decreased in : Aplastic Anaemia.

Haemolytic
like
Hypersplenism
Haemolytic
like
Hypersplenism

NB. Reticulocytes correction = reticulocyte X patient PCV / normal PCV
Reticulocyte index = reticulocytes correction / 2

4) Peripheral blood film: Size - Shape - Abnormal bodies - Others

SHAPE : Biconcave

SIZE : 2.5 um * 7.5 um

Abnormal size:-

- Microcytic : e.g. Iron deficiency anaemia
- Macrocytic : Megaloblastic - non-Megaloblastic
- Anisocytosis : non specific

Abnormal shapes:-

1- Target (Leptocytes - Mexican hat cells) :

- Thalassemia
- LCF
- Obstructive Jaundice .
- After splenectomy

2- Acanthocytes (Spiky RBCs) :

- Abetalipoproteinaemia
- α -thalassaemia trait

3- Spherocytic :

- hereditary Spherocytosis
- Autoimmune
- hemolytic Anemia

4- Schistocytes (Fragmented RBCs):-

- Thrombotic
- thrombocytopenic purpura
- hemolytic uremic syndrome
- mechanical damage

5- Stomatocytes (Fragmented cells): membrane defect

6- Tear drop : Myelofibrosis

7- Sickle : sickle cell anaemia

8- Burr cells (Irregular RBCs) : uraemia

9- Elliptical : membrane defect

10-Spur cell : LCF - after splenectomy

11-Poikilocytosis : Variable (non-specific)

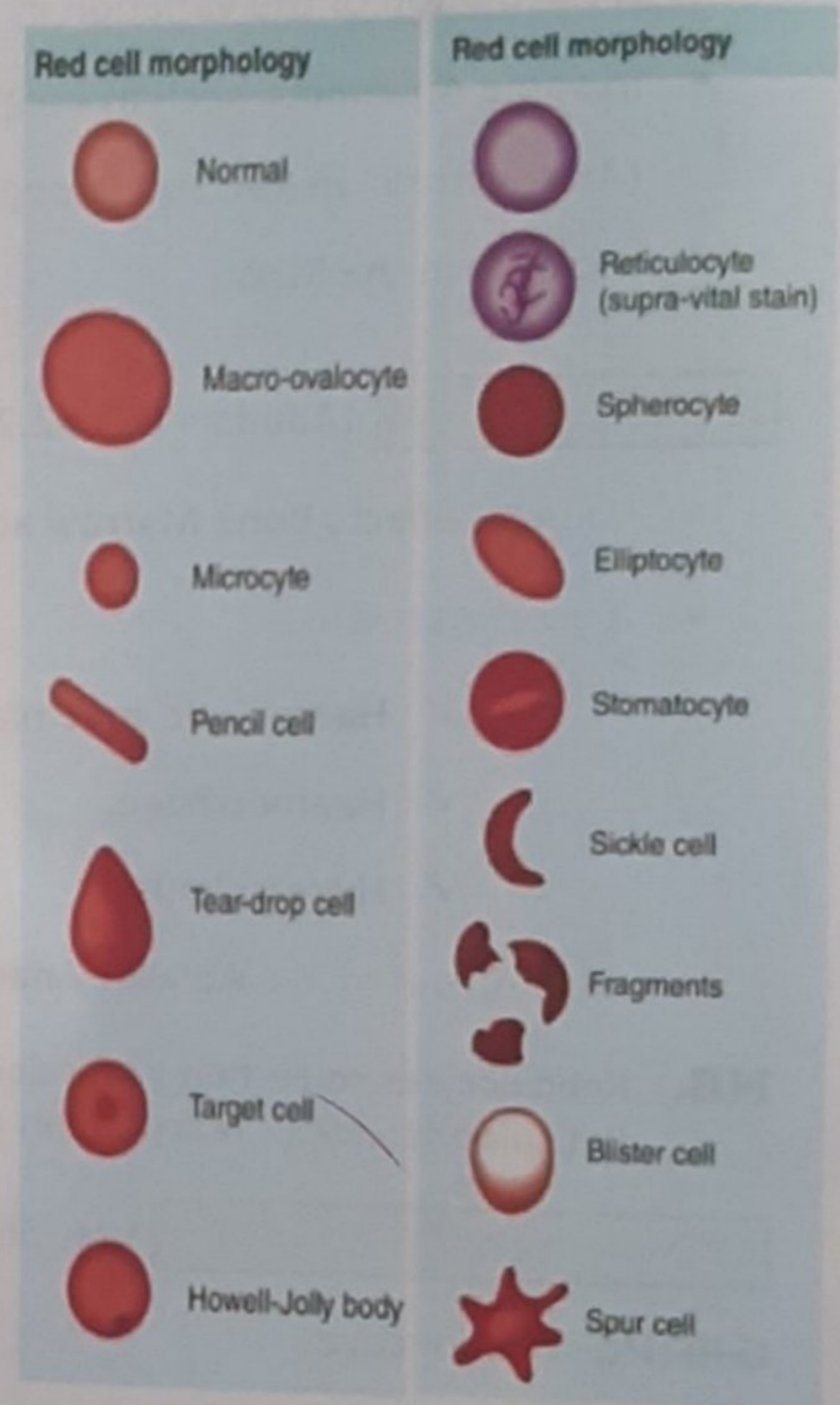
Abnormal bodies :

1- Howell Jolly bodies (Nuclear remnant):

- post splenectomy
- Megaloblastic
- leukaemia (rare).

2- Heinz bodies:

- oxidized hemoglobin
- Enzyme deficiency hemolytic anemia : G6PD & pyruvate kinase deficiency



3- Pappenheimer bodies (Granules) *RBC contain granules of Iron in circulation*

- Sideroblastic *in correlation bet iron & protoporphyrin in RBC inside bone marrow.*
- after splenectomy

Others

1. Parasitized RBCs : malaria
2. Stippling basophile dots : immature cytoplasm released in cases of accelerated erythropoiesis

- lead poisoning
- thalassaemia.

3. Rouleaux

- stacked/clumped groups of red cells
- Caused by increased acute-phase proteins
- Associated with high ESR:- infections - autoimmune conditions.

4. Leuco-erythroblastic

- (increased immature cells = myeloblasts or normoblasts)
- BM infiltration: metastatic malignancy
- prolonged hypoxia - severe infection.

5- Bone marrow examination :

	Aspiration	biopsy
Advantages	- Fast - Gives relative quantity of different cells	- Gives cell and stroma constitution. - Represents all cells
Disadvantage	- Doesn't represent all cells - May give no blood cells (dry tap).	- Slow processing

VALUE FOR DIAGNOSIS :

- 1- Hypo cellularity : Aplastic anaemia
- 2- Hyper cellularity of normal cells : haemolytic anemia – leukaemoid reaction
- 3- Hyper cellularity of abnormal cells : leukaemia - multiple myeloma
- 4- Excessive fibrosis : myelosclerosis
- 5- Detection of abnormal cells : sideroblastic
- 6- Others : ratio of myeloid to erythroid (M:E ratio)

CONTRAINDICATIONS

- **Absolute** : severe bleeding disorder (coagulopathy) but, can be safely performed in cases of thrombocytopenia.
- **Relative** : skin or soft tissue infection over the hip

NB. Aspiration doesn't always represent all cells since e.g. lymphoma stick to the trabecula, and would thus be missed by a simple aspiration.

yl

ANEMIA

The term anemia is derived from Ancient Greek for "bloodlessness"

Definition

Anemia is a decrease in RBCs mass that can be detected by :

- ↓ total blood hemoglobin concentration
- ↓ RBCs count.
- ↓ Haematocrit value below the normal range for age and sex of the patient.

↓ Hb
↓ RBC
↓ PCV Hematocrit value

Hb
RBC
PCV

Laboratory defined as : hemoglobin less than 12 g/dL or Hematocrit value less than 37 cl/L

Hb < 12
PCV < 37

Physiological compensation for decreased RBCs mass

1. Decreased haemoglobin oxygen affinity
2. Redistribution of blood flow
3. Increased cardiac output (stepped changes):-
 - Decreased peripheral vascular resistance
 - Decreased blood viscosity
 - Anemia must be fairly severe (Hb < 7 g/dL) before cardiac output rises.

Scheme

Clinical picture

- May be asymptomatic : usually with anemia of gradual onset (good compensatory mechanisms)
- Symptoms (Non-specific)
 - 1) General: easy fatigability - fainting - headache. EFH
 - 2) Neurological: intermittent claudication - tinnitus - numbness INT
 - 3) CVS: dyspnoea on exertion - palpitations - angina dPA
- Signs

Non-specific :

- General : Pallor
- CVS : - Hyper-dynamic circulation - Tachycardia.
- systolic ejection murmur (anaemic HF) - S3 gallop.
- In Rapidly developed anemia : orthostatic hypotension , orthostatic

" Aortic murmur
et. Pulmonary area
& Aortic area

tachycardia and Heart failure may occur

Specific features

- Chronic anemia : may result in impaired growth in children
- iron deficiency anemia : Spooning of nails ☞
- hemolytic anaemia: Splenomegaly- jaundice - leg ulcers - skeletal changes.

NB : Clinical picture of anemia depends on the duration of the disease and to lesser extent on the severity of the diseases

- An acute hemorrhagic anemia manifested at 20% loss of blood volume
- Conversely in anemias developing over long periods effect of compensatory mechanisms may delay the clinical manifestations

Classification of anemia

❖ Erythrokinetic Classification

سأشعر

i. ↓↓ cell production :

1. **Hb** : - Iron deficiency - Thalassemia
- Anemia of chronic disease
2. **DNA** : Megaloblastic anaemia
3. **Stem cell** : - Aplastic anemia
- Myeloproliferative disorders
4. **Bone marrow Infiltration** : Carcinoma , Lymphoma
5. **Toxic injury** : - Radiotherapy , Chemotherapy
6. **Infection** :

ii. ↑↑ Red cell destruction : Haemolytic anaemia

iii. ↑↑ Blood loss :

- May caused by GIT bleeding (Ulcers, Ankylostoma ...etc)
- heavy menstrual periods or long term overdose of aspirin.

❖ Morphological Classification.

i. Microcytic hypochromic Anemia : (low MCHC & low MCV)

- Iron deficiency anemia *نقص الحديد*
- Thalassemia
- Sideroblastic *some anemia of chronic illness*

ii. Normocytic normochromic Anemia : (Normal MCHC, normal MCV)

- Anemia of chronic disease
- Hemolytic anemia
- Anemia of acute hemorrhage
- Aplastic anemia

There is nothing called hyperchromic anemia

iii. Macrocytic Anemia : (normal MCHC & high MCV).

- Megaloblastic :
 - vit B 12 deficiency
 - folic acid deficiency
- Non megaloblastic :
 - liver diseases
 - Alcohols
 - hypothyroidism
 - myelodysplasia

Investigations for anemia

A- For Diagnosis of Anaemia

- CBC :
 - ↓↓ "RBCs & Hb"
 - WBCs & Platelets → Vary according to the type of anaemia
 - Reticulocytes : high in hemolytic anemia

- ESR : ↑↑ *غازل الدم لوعده*

B- Type of anaemia

Correction of ESR = $\frac{Age+10}{2}$ for female & $\frac{Age}{2}$ for male

Ex: Female 50 age & Hb = 10
 $\therefore ESR = \frac{50+10}{2} + 20 = 50$

every decrease 1 degree in Hb = 10

Depends on cell size and Hgb content (RBCs indices as MCV & MCHC) .

Microcytic hypochromic	Normocytic normochromic	Macrocytic
↓ MCV	Normal MCV	↑ MCV
↓ MCH	Normal MCH	Normal MCH
↓ MCHC	Normal MCHC	Normal MCHC

C- Further investigation : For the etiology as hemolytic anemia , bleeding and Examination.

IRON METABOLISM

- Iron is obtained from Red meat, liver and egg yolks. Flour, bread, and some cereals.
- Absorbed primarily in the **duodenum** & Only **ferrous** iron can be absorbed.
- Its absorption is increased by Reducing agent as **Vit. C** & Decreased by (Antacids, Oxalate, Tetracycline, Phosphate, phytate & tannic acid.)
- Transport : Iron is transported by **transferrin** (carrier protein) to the BM where it is incorporated into heme molecules.
- Store:- Excess iron is stored in liver, spleen and the mononuclear Phagocyte system (macrophage)
- The storage forms of iron are: ferritin and hemosiderin.

- Iron needs HCL to be converted from ferric Fe^{+3} to ferrous state Fe^{+2} to be absorbed
- **FERRITIN** : Water-soluble molecules, present in plasma in concentration equal to ferritin molecules in histiocytes, therefore, decreased iron stores are reflected by decreased serum concentration of ferritin
- In bone marrow histiocytes iron stored as hemosiderin.
- **SIDEROBLASTS** are RBC with excessive iron stores - stained with Prussian Blue stain.
- **RECYCLING**:- Fe has a recycling properties, so in hemolysis, no Fe loss except in PNH.

IRON PROFILE

1) Serum iron	Free Iron available in the serum for erythrocyte production. (Not related to body stores as ferritin)
2) Serum ferritin <i>acute phase reactant</i> <i>منخفض بتأثير بيت</i>	- soluble storage form (proportional to iron stored in tissues) - (male=15-400 ng/ml - female=10-200 ng/ml) - (1 ng/ml = 10 mg of store)
3) Total iron binding capacity (TIBC) <i>المرتفعة الحادة</i>	- A measure of transferrin which is <u>not bound</u> to iron. - The TIBC is <u>inversely</u> related to iron level
4) Saturation of transferrin <i>انخفاض الشغل</i>	- Calculated by dividing the serum iron by the TIBC. - More accurate test than serum iron but not as ferritin.
5) Serum transferrin <i>انخفاض</i>	- Measured by EIA (enzyme immunoassay). - Serum transferrin values correlate well with TIBC values

IRON DEFICIENCY ANEMIA

Etiology: 2 DECREASE & 2 INCREASE

i. Decreased intake :

- infants of 6 months.
- starvation
- anorexia
- dysphagia : as Plummer vinson \$

ii. Decreased absorption :

- Achlorhydria (gastrectomy)
- malabsorption syndrome
- excess intake of : phytate , Antacids , tannic acid (tea).

" All $\downarrow$ HCL thus $\downarrow$ iron conversions to its absorbable state Fe^{+2} "

iii. Increased demand :

- During puberty ($\uparrow$ body requirement)
- Pregnancy

iv. Increased blood loss :

- GIT causes :

- ✓ Esophagus : cancer , varices , ulceration
- ✓ Stomach : Excess NSAIDs , gastric ulcer , cancer stomach
- ✓ Intestine : cancer colon , ulcer , ancylostoma dueudenale , anal fissures or bleeding hemorrhoids .

- Non GIT Causes :

- ✓ Repeated blood donation
- ✓ Excessive menstruation
- ✓ Hematuria
- ✓ Epistaxis...

Clinical Picture

A) As general features of anemia (see above)

B) Type of patient (High-risk groups)

1- Women :

- Women, in general, have smaller stores of iron than men and have increased loss through menstruation
- child-bearing age (blood loss through menstruation)
- Pregnant women

2- Infants - children (rapid growth phases)

3- People with a poor dietary intake (no meat or eggs for several years).

C) Epithelial changes (defect in Fe enzymes)

- 1- Mouth : Atrophic (Sore & smooth tongue) & Angular stomatitis
- 2- Esophagus : Post-cricoid web (plummer vinson syndrome)
- 3- Stomach : Atrophic gastritis
- 4- Nails : brittle - spooning (Koilonychia)
- 5- Hair : Dry loss of luster + Hair loss

D) Pica : perverted appetite

E) Features of the cause :

- ✓ Anklystoma : GIT upset & **PICA**
- ✓ Plummer Vinson : dysphagia *female middle age -
PreCancerous with splenomegaly
+ atrophy in Gastric Mucosa.*

A-Diagnosis of Iron deficiency anemia:

➤ For diagnosis of IDA

1- CBC : picture of Anemia (micro-hypo) *↓ Hb ↓ MCV ↓ MCHC*

2- Iron profile : (All are ↓ except TIBC ↑)

- Serum iron : Decreased
- Serum ferritin : Decreased
- Total iron binding capacity (TIBC) : **Increased**
- Saturation of transferrin : Decreased

3- Bone marrow examination :

- Erythroid hyperplasia
- Not important & not needed in diagnosis

➤ For determination of the aetiology

1. Stool analysis : ova - blood - occult blood

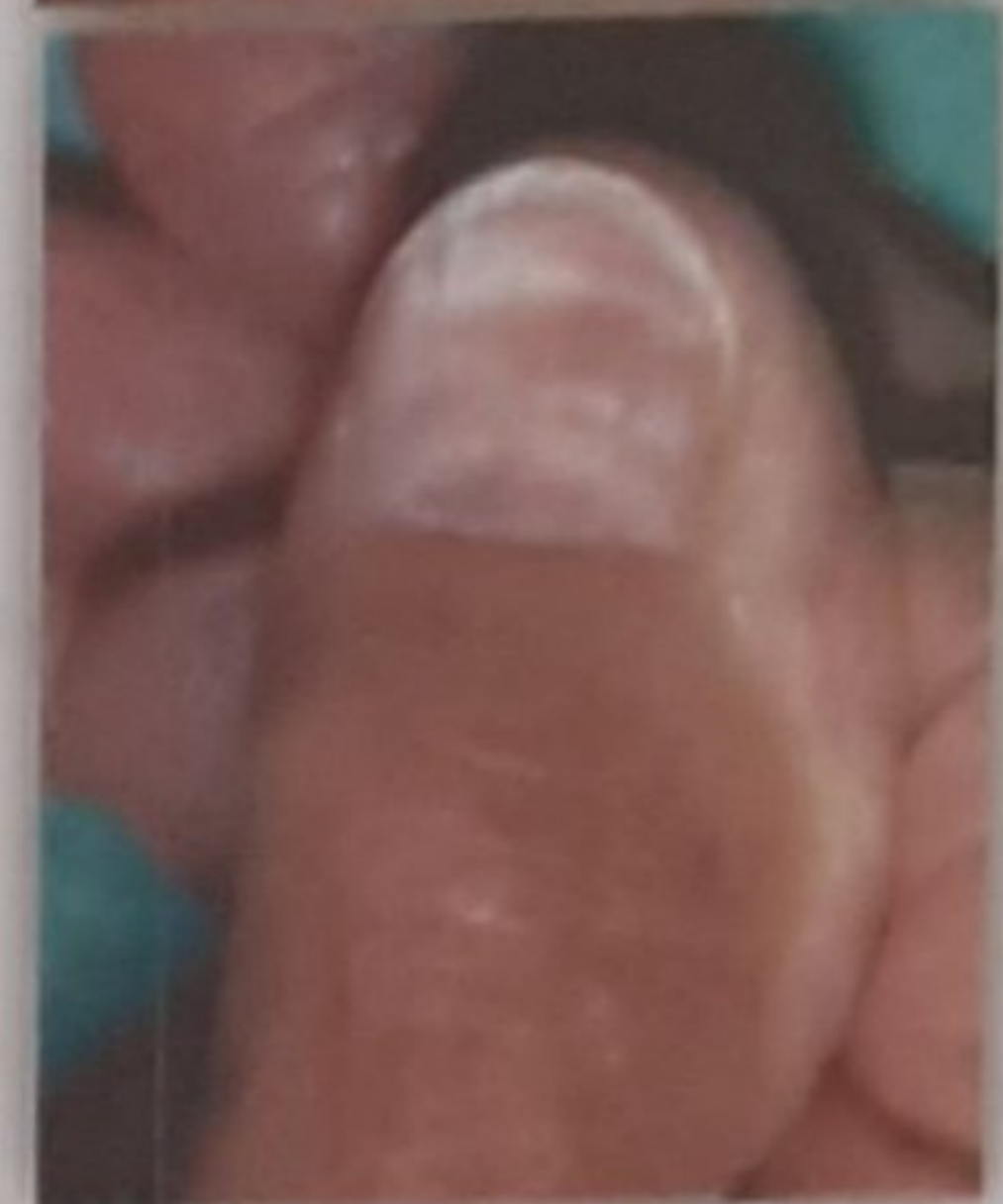
2. Upper endoscopy - Laryngoscopy : (Plummer vinson) *dysphagia* *Post Cricoid web*

Treatment

A) Treatment of the cause :- e.g. treatment of Anklystoma

B) iron therapy :

Aim → correction of hematocrit value within 2 months.



Remember Normal values

- 1- Serum Iron
(50 - 150 ug / dl)
- 2- Serum ferritin
Male=15-400 ng/ml
Female=10-200 ng/ml
- 3- TIBC
(250 - 370 ug / dl)
- 4- Saturation of transferrin
(25 - 50 %)



shedding of epith. → Forming Post
cricoid web
↓
dysphagia

Oral iron

Parental iron

Forms

- ✓ Ferrous sulphate:- 200 mg tabs
- ✓ Ferrous gluconate 300 mg tabs

تحت العلاج
بالحديد
أو ثلاثة

Forms

- ✓ Fe dextran 100 mg/d IM / iv
- ✓ Fe sorbitol 50 mg/d

على الحول وتخطيه
لأنه حساسية
phosphatase
change

Recommendations

- Preferred on an empty stomach
- Milk and antacids should not be taken
- Vitamin C is recommended / ↑ absorption

Side effects

- GIT upset, Diarrhea & Constipation
- dark stool

Indications

- GIT upset
- Malabsorption
- Rapid correction

Side effects :

- fever, hypersensitivity
- abscess, thrombophlebitis
- pigmentations.

- Iron should be continued for another 6-12 months to replenish the body's store.

C) in severe cases : blood transfusion or packed RBCs.

الحديد

Sideroplastic Anemia

Definition :

Abnormal production of RBCs due to incorporation of iron with protoporphyrin leading to:

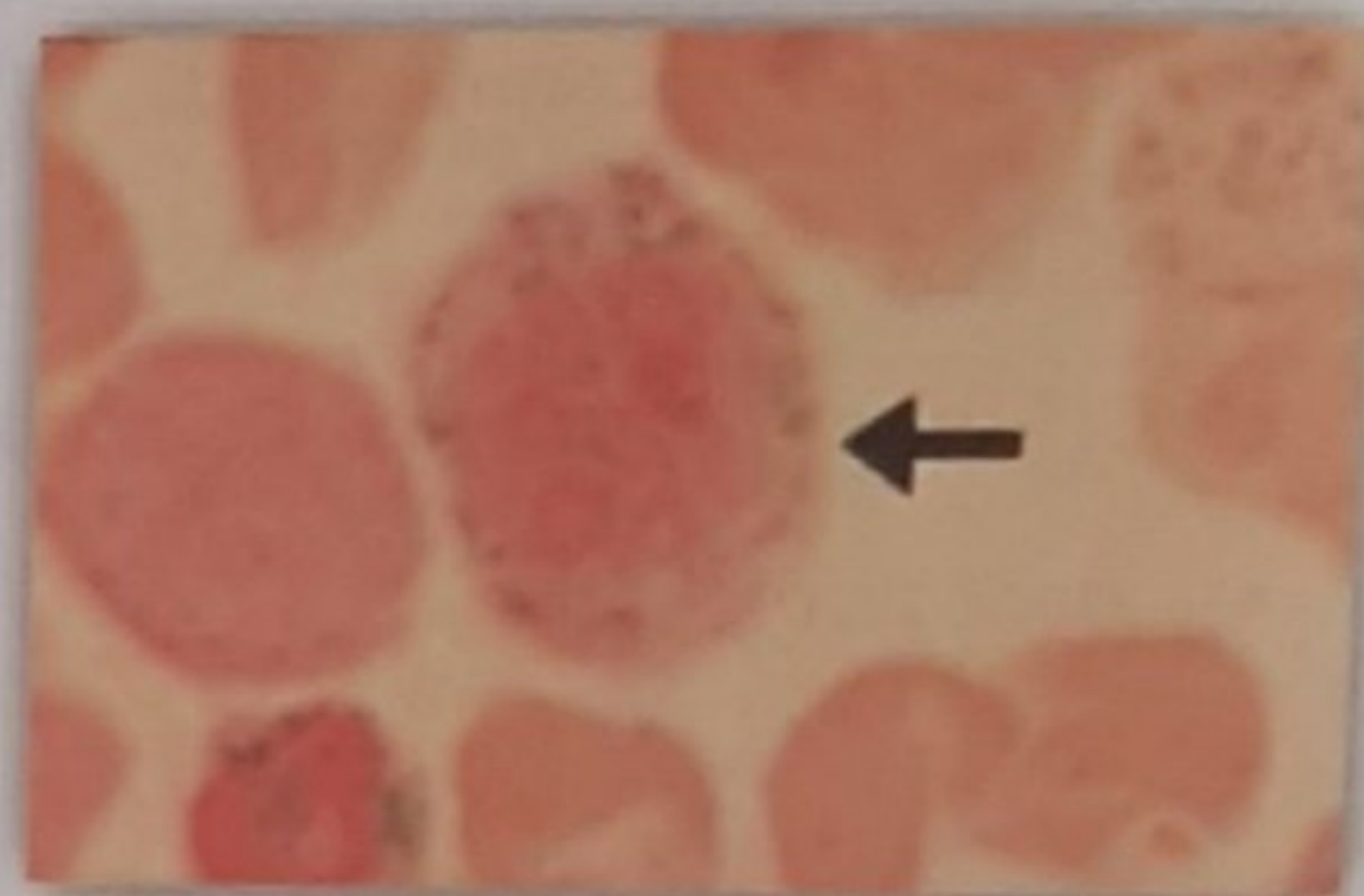
- Failure of haeme synthesis
- Deposits of iron in the mitochondria that form a ring around the nucleus of the developing red blood cell.

Causes :

1) Hereditary : May be X linked or autosomal.

2) Acquired:

- Primary: part of myelodysplastic syndrome
- Secondary: developed after birth
 - Toxins: lead or zinc poisoning
 - Drug: ethanol, INH, chloramphenicol, cycloserine
 - Nutritional: pyridoxine or copper deficiency
vit B₆



Investigations:

CIP / as any anemia - scheme. Refractory

1- CBC and RBCs indices :- ✓ <u>Anaemia</u> usually microcytic hypochromic ✓ Leukocytes and platelets = <u>normal</u>.	2- Peripheral blood film ✓ Marked <u>anisocytosis</u> and <u>poikilocytosis</u>. ✓ Basophilic <u>stippling</u> + target cells ✓ <u>Pappenheimer</u> bodies are present. <i>diagnostic</i>
3- Bone marrow (diagnostic) ✓ Erythroid <u>hyperplasia</u> with maturation arrest. ✓ <u>Ringed sideroblasts</u> (signet ring) stained with Prussian Blue ✓ <u>Hemosiderin</u> is increased.	4- Iron profile:- ✓ Serum iron, saturation and ferritin = increased. ✓ TIBC = normal to decreased.

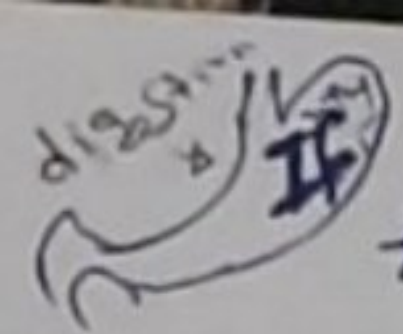
Treatment :

As general role of any Anemia plus :

- Pyridoxine (Vitamin B₆) for Hereditary form
- Bone marrow transplantation

Sideroblast = Pappenheimer
in B.M. | in blood.

absorption
(~~not~~)



*vit B₁₂ Present in animal source

need Intrinsic factor & Terminal Ileum To be digested and absorbed

*Folic acid Present in Plant source easy digested and absorbed from any part of GIT

Dr/M. Allam

Megaloblastic Anemia

Anemia developed due to vit b 12 or folic acid deficiency leading to pancytopenia & macrocytosis

Pathophysiology

A) Nucleo - Cytoplasmic asynchrony

- Arrest of Nuclear maturation → Delayed cell division → Large cells (↑ MCV)

B) Intra-Medullary hemolysis

- Megaloblastic cells destroyed in the B.M → Pancytopenia + increase iron and Bilirubin

The key problem is a block in DNA synthesis owing to defect in methylation.

Aetiology

A- Deficient intake of B 12 OR Folic Acid

- Old Age
- Starvation "prolonged"
- Alcohol Intake
- Poor Socioeconomic state
- Anorexia
- Vegetarian → ↓ vit B₁₂

Liver → store vit B₁₂ for 2-5 yr
store folic acid for 2-3 months

B- Deficient absorption

➤ Deficient intrinsic factor :

- * Pernicious anemia - anti Parietal cells antibodies - or anti intrinsic factor antibody
- * Gastrectomy

➤ Structural abnormalities :

- Diverticulosis - aneurysm of Colon
- Fistula
- Achlorhydria
- Intestinal anastomosis
- Ileal resection and bypass
- Jejunal resection
- * Diphyllobothrium latum Present in Terminal Ileum
- Chronic pancreatitis
- Tropical sprue multi organisms (Combined vit. B₁₂ & folate def.)
- Selective B₁₂ malabsorption (Congenital and drug induced)

C- Increased demand

- Dialysis
- infants
- cirrhosis → ↓ storage
- Prolif. Cells
- Pregnancy
- Drugs :

- 1- Anticonvulsants (phenytoin)
- 2- Pyrimethamine
- 3- Trimethoprim

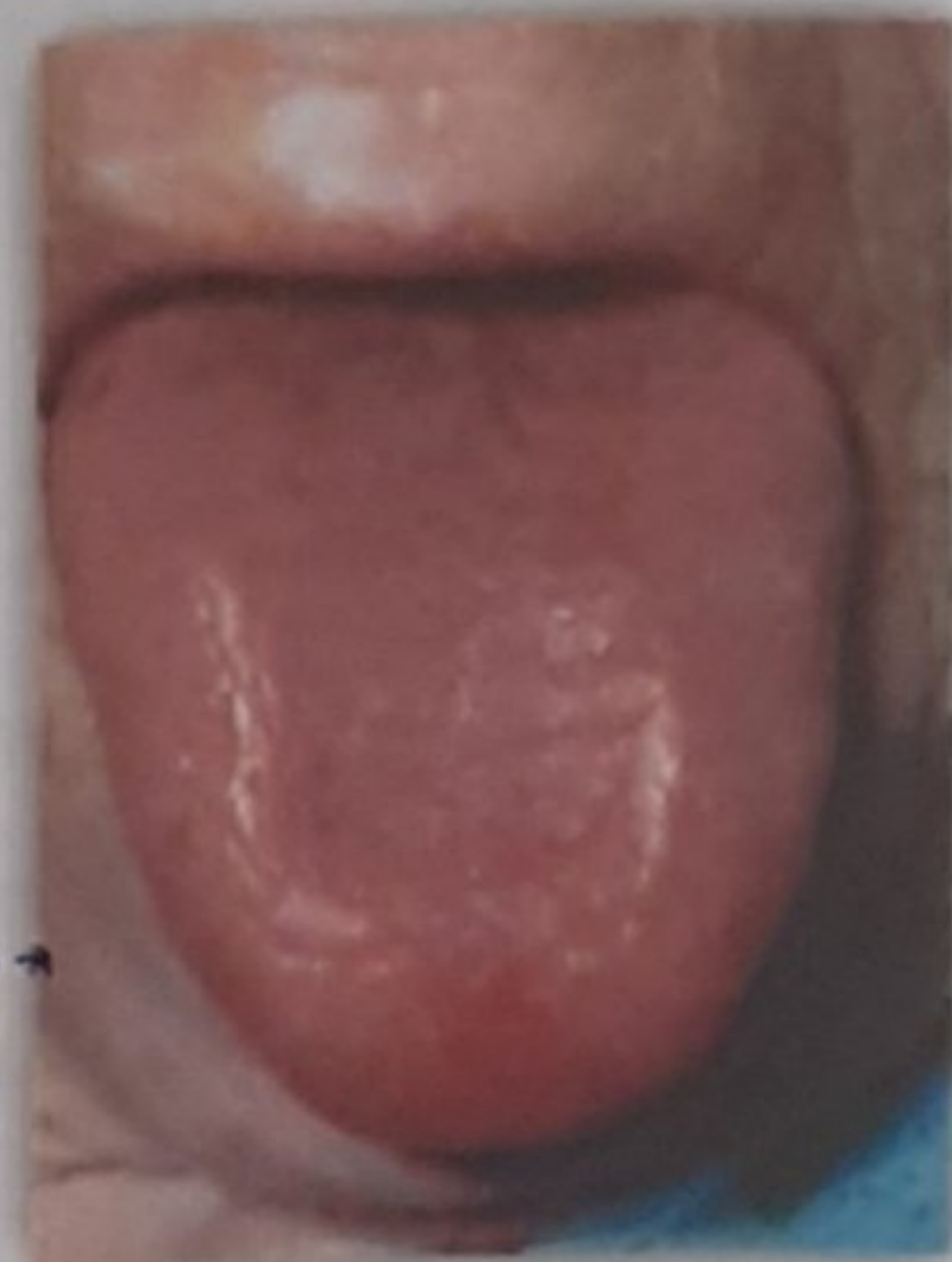
- 4- Folic acid antagonists : methotrexate ^{TPP of} - Rheumatoid, Anti Cancer.
- 5- Purine antagonists : mercaptopurine
- 6- Pyrimidine antagonists : cytosine-abinoside

Clinical pictures

1) **Anaemia**:- As general features of anemia

2) **GIT** :- (A trophy of epithelium)

- Tongue:- Red & swollen (Beefy tongue)
- Stomach:- Nausea, vomiting, dyspepsia (Achlorohydria)
- Intestine :- Diarrhea ^{المساقي} ~~malabsorption~~ ^{متلازمة سوء الامتصاص} Synd.
- Organs :- Hepatosplenomegaly ^{تضخم الكبد والطحال} ~~Extra medullary haemopoiesis~~



3) **Neurological manifestation** :- (defects in Myelination)

- Posterior Column defect ^{- deep sensation}
 - Pyramidal tract defect ^{motor}
 - Poly neuropathy ^{peripheral neuropathy}
- Handwritten notes:*
 - only in Vit B₁₂ deficiency
 - in Vit B₁₂ only
 - Subacute combined degeneration - early reversible IF not TTT → Irreversible
 - or TTT by Folic acid only → Folic acid → maturation of DNA → exhaustion of Vit B₁₂ → neurological lesion.

4) **Complications**

- Neurological lesion may be irreversible if treatment is not initiated within 6 months of the diseases onset
- False positive pap smear (affects the maturation of all epithelial cells). ^{in cervix of uterus}

Investigations

A) **Diagnosis of anaemia** :- (Pancytopenia)

- CBC → RBCs, Hb%, PCV : decreased
- ESR → increased
- Platelets → thrombocytopenia
- WBCs → Leucopenia

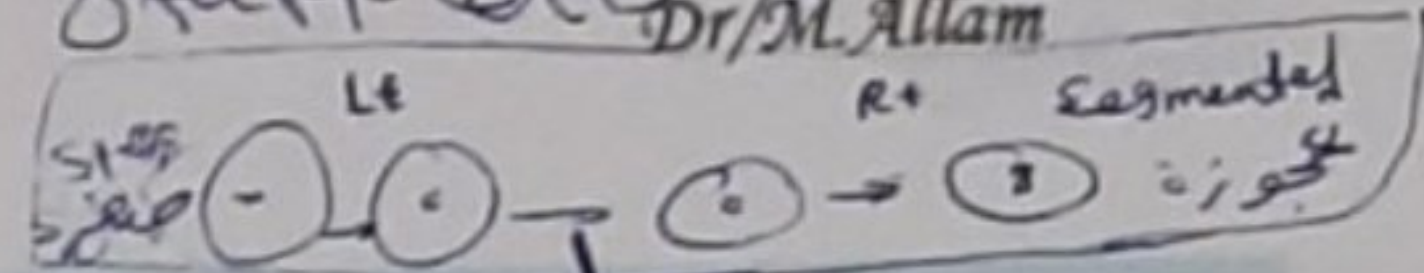
B) **Type of anaemia** :

- CI & MCV → increased
- Macrocytic normochromic
- MCHC → Normal

C) **Detection of megaloblastic changes**

- 1- Blood film : Howeli - Jolley body ± Anisocytosis & Poikilocytosis ± Ovalocytes.
- 2- BM aspiration : Megaloblastic (diagnostic).

Hematology NB/ WBC Staff To segmented cells = $\frac{1}{5} - \frac{1}{10}$
 in Megaloblastic anemia: Bone marrow can't produce staff cells so staff to segmented cells are shifted to R+
 Dr/M. Allam



NB. Megaloblastic cells : large cells with large immature nuclei (delayed nuclear maturation due to defective DNA synthesis) + excessive hemosiderosis.

NB. Reticulocytes are usually absent (but may be also normal)

3- Evidence of haemolysis : Bilirubin & LDH : increased.

D) Detection of the cause

Vit.B-12 deficiency	Folic acid deficiency
- Serum B12 : less than 100 ng/ml (Normal = 200: 900 ng/ml) - Gastric function tests - Serology : anti-parietal cell antibody (pernicious anemia) - Increased homocysteine and methyl malonic acid	- Serum folic : less than 4 ng/ml (Normal 6-20 ng/ml). - Increased homocysteine

التاريخ

Schilling test

Was performed previously to determine the nature of the vitamin B12 deficiency but, it is now largely a historical artifact.

- 1- Vit B12 (1000 mg) IM (for restoring the defect)
- 2- Oral radioactive B12 (Normally 25% of it excreted via the kidney)
- 3- Reduction in the urinary excretion means malabsorption (less than 5%)
- 4- Correction of defect in 3 trials
 - a) Correction after intrinsic factor oral means pernicious
 - b) Correction after antibiotic means bacterial over growth
 - c) Correction after pancreatic enzyme diagnosed as pancreatic defect

Treatment

• Prophylaxis :

- ✓ Vit B : for gastrectomy , short gut , diabetes , pregnancyetc.
- ✓ Folic acid : hemolytic anemia.

• Therapeutic

- Treatment of the cause
- Vit.B12

deficit.

Route	Replacement therapy	Maintenance therapy
IM	1000 micro gm/day for 5 days Then weekly for 4 w	1000 micro-gm / week For 3 months
Oral	1000 : 2000 micro-gm /day	25 : 100 micro-gm daily
Nasal <i>or sublingual - deficit.</i>	1500 micro-gm weekly for 4 w	500 micro-gm weekly

- Folic acid : Replacement therapy as 5 Mg / day (oral) after correction of anaemia
Maintenance dose as 1mg / day may be used

NB. Monotherapy by folic acid initially improve anemia and GIT manifestations but aggravates the neurological defects as vit b12 is needed for activation of folic acid into folinic acid

PERNICIOUS ANAEMIA (ADDISONIAN ANAEMIA)

- defective absorption of vit B12 caused by immunological absence of Intrinsic factors.
- Immunological absence of Intrinsic factors by two mechanisms:-

1- Anti Parietal cell antibodies (APCA)

- 90% of patient
- Gastric atrophy and reduction of HCL

2- Intrinsic factor antibodies : blocking or precipitating
50% of patient

• clinical picture :

- Common in Elderly
- Females More than males
- Associated with other Autoimmune Diseases.
- Detected with HLA A3 + B7.
- As C/P of Megaloblastic anemia

*elderly
♀ > ♂
+ other autoimmune dis.
HLA A3+B7*

➤ Investigations : As Megaloblastic anemia plus

- Gastroscopy and biopsies : atrophic gastritis
- Detection of the Autoantibodies (APCA) (AIFA)
- Gastric function test.

III / Parenteral vit B12

Aplastic anemia

Bone marrow failure

Definition

Reduction of bone marrow activity, usually presented by pancytopenia or selective ~~or selective~~ aplasia of one or more of elements

Aetiology & Classification:

Pleuri-potent defect : Pancytopenia

Uni-potent defect $\rightarrow$ $\downarrow$ RBC $\rightarrow$ $\downarrow$ Platelet $\rightarrow$ TAR $\rightarrow$ absent Radius

Fanconi anemia $\neq$ Fanconi syndrome of kidney

Causes

1) **Idiopathic** : Immunological - T cell activities.

2) **Congenital** :
- Fanconi anaemia
- Familial aplastic anaemia

- Autosomal recessive
- Pancytopenia
- Skeletal deformities
- Susceptible to leukaemia

3) **Secondary to:**

a. **Irradiation**

b. **Infection**: hepatitis / IMN $\rightarrow$ Infectious mononucleosis

c. **Iatrogenic**: Phenytoin, chloramphenicol, chlorpropamide, chlorambucil & carbimazole (anti T3).

d. **Immune**: SLE

e. **Infiltration**: Leukaemia, Lymphoma, T.B & Metastasis.

f. **PNH** (see above) $\rightarrow$ Paroxysmal nocturnal hemoglobinuria

g. **Liver transplantation** for fulminant hepatitis

h. **Eosinophilic fasciitis**.

ERYTHROCYTE APLASIA

RBC $\rightarrow$ Monoplasia

1- **Congenital** : Diamond - Blackfan "tri thumb"

2- **Acquired** : Para malignant \$ - Aplastic crisis of hemolytic anemia - CRF - Thymoma

Malignancy secrete Antigen or antibodies
Reach to BM. not malignancy itself.

Thymus gland
Chronic Renal Failure

MEGAKARYOCYTIC APLASIA

Platelet

1- Thrombocytopenia absent radius [TAR]

2- Other rare congenital : Hair hypoplasia / Shwachman-Diamond \$ / Diamond-Blackfan syndrome / Dyskeratosis congenita

Clinical picture

1- Features of anaemia (as above)

2- Granulocytopenia;

Recurrent infection as Sore throat, Stomatitis, Ulcers - Fungal infection

3- Thrombocytopenia: as Purpura (see later)

Investigations

CBC :

- RBCs : Normocytic normochromic anemia
- Reticulocyte : absent (diagnostic)
- WBCs : leucopenia with relative lymphocytosis
- Platelets : Thrombocytopenia

BM :

- Hypoplasia or aplasia
- Detection of the cause as in myelophthestic anaemia

Treatment

a) Treatment of the cause

- Stop medication which may cause BM aplasia
- Immunosuppressive in idiopathic of T-cell induced Aplastic anemia.

b) Supportive therapy

- Anemia:- blood transfusion
- Thrombocytopenia:- fresh blood transfusion .
- Granulocytopenia:- isolation of the patient - Treatment of infection
- G-CSF (granulocyte- colony stimulating factor) *stimulate WBC synthesis.*

c) BM transplantation

d) BM stimulant

- Androgen.
- Prednisolone. *"cortisol"*
- Recombinant erythropoietin (EPf)
- G-CSF (granulocyte- colony stimulating factor)

Differential diagnosis of A.anemia

Other causes of pancytopenia (see above)

Hemolytic anemia

Definition

Shortening of RBCs life span usually accompanied with BM over activity

Pathophysiology :

A- Effect of Haemolysis

- Short life span of RBCs : Anaemia , Jaundice & Gallstones (↑ bilirubin)
- BM Overactivity : Skeletal changes
- Extra medullary erythropoiesis : hepato-spleno-megaly
- iron overload
- Crisis may occur.

B- Site of Hemolysis.

Extra-vascular (90%)	Intra-vascular (10%)
Usually blood in sinusoids of spleen	Release of Hb in blood stream
▪ Hemolytic jaundice ▪ Indirect bilirubin ▪ High stercobilinogen & urobilinogen ▪ Normal colour of urine (Acholuria)	▪ Haemoglobinemia ▪ Haemoglobinuria (Dark urine)

- PNH
- G6PD deficiency

Classification of hemolytic anemia

or = Aetiology

Corpuscular defects	Extra-corpuscular defects
1- Membrane defects <i>all hereditary except PNH</i> ▪ Hereditary spherocytosis <i>Autosomal dominant</i> ▪ Paroxysmal nocturnal hemoglobinuria (PNH) <i>acquired</i> 2- Hb Defects ▪ Thalassemia ▪ Sickle cell anemia <i>HbS</i> 3- Enzyme defects ▪ G6PD deficiency <i>X-linked</i> ▪ Pyruvate kinase deficiency <i>RECESSIVE</i>	1- Immunological <i>All are acquired</i> ▪ Allo-immune : ABO Incompatibility ▪ Auto-immune : Warm & Cold Antibodies 2- Drug induced 3- Infections : malaria 4- Toxins : snake Venom 5- Mechanical : Prosthetic valves, calcific valve, Microangiopathy, march hemoglobinuria <i>عن طريق المشي</i> 6- Hypersplenism <i>extra vascular</i>

*all intravascular except:-
Hypersplenism.*

- All corpuscular Causes are **Hereditary** except PNH
- All corpuscular Causes are **Extravascular** except : PNH, G6PD def., & Hemolytic crisis.
- All Extracorpouscular causes are **Acquired**
- All Extracorpouscular causes are **intravascular** except Hypersplenism

📖 Markers of intravascular hemolysis

- 1- Haptoglobin : (Hb carrier) **Decreased**
- 2- Hemopexin- Hb carrier (oxidized Hb) : **Decreased**
- 3- Hbaemia : **Elevated**
- 4- Met-haem albumin (Hb carried on albumin): **Detected**
- 5- Hburia - Haemosiderinuria : **Detected**

Clinical presentation

Scheme +

- 1- **Jaundice** : Lemon yellow
- 2- **Stool** : Dark (increased sterchobilinogen)
- 3- **Urine**: Normal colour (Acholuric jaundice)

Except:-

- 1- With standing
- 2- At hemolytic crisis *Intravascular haemolysis → Haemoglobinuria*
- 3- If accompanied with gall stone obstructive jaundice

4- **Hepatosplenomegaly** :

- **Hepatomegaly** : iron deposition + extra medullar erythropoiesis
- **Splenomegaly** : extra vascular haemolysis

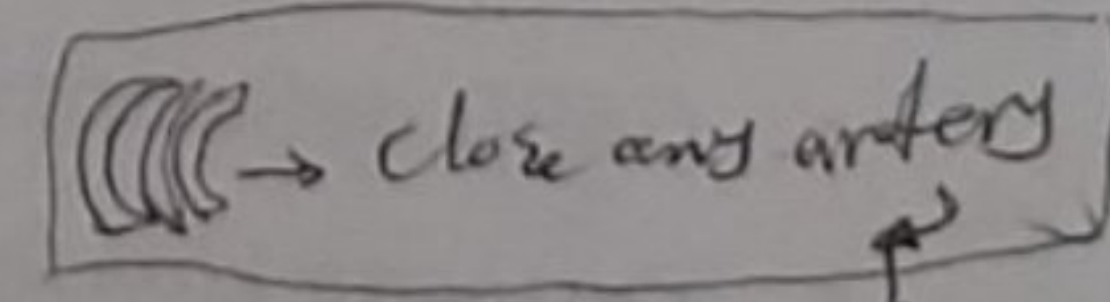
5- **Mongoloid face** (BM expansion)

- ➔ = Frontal bossing, prominent facial bones and dental mal-occlusion
- ➔ Explained as; maxilla may overgrow, prominence of the upper incisors, and separation of the orbit.

6- **Gall stone** (pigment stone)

7- **Leg ulcers** : mainly with sickle cell anaemia

Sickling or infarction



8- **Crisis** : 3 types of crisis may occur (megaloblastic, hemolytic, vaso-occlusive) .

distorted spleen

+ Autosplenectomy

1- Haemolytic crisis
 - Intravascular
 - Expansion
 Hematology
 Pyroan
 reticulocyte → ↑

2- Aplastic crisis: - acute bone marrow failure - Reticulocytopenia
 Pancytopenia

Dr/M. Allam

Types of crisis in hemolytic anemia

- 3 - Megaloblastic crisis: - ^{Gradual} due to increased demand for folic acid, usually of gradual onset.
 - marked by Pancytopenia and Megaloblastic features (as above).
 - Presented by nit B₁₂
- 4 - Sequestration crisis: - ^{الرجعة الليفية} pooling of blood in splanchnic area usually presented by shock and abdominal pain.
 Extra vascular
- 5 - Vaso-occlusive crisis: - Mainly in sickle cell anemia.
 (التهلكة في الدم)

Investigations

i) Diagnosis of anemia:

- CBC → - RBCs, Hb%, PCV : Decreased
 - WBCs & platelets : Increased (BM hyperactivity)
- ESR : Increased Except sickle cell anemia

* normocytic normochromic except thalassemia
 microcytic hypochromic
 صيرف في سبب لونها
 Sickling alone

ii) Diagnosis of Hemolysis: "All are Increased"

- Reticulocytosis: Except in aplastic crises or Megaloblastic crisis
- Bilirubin: Increased mainly indirect
- Urinary Urobilinogen: Increased
- Fecal Sterchobilinogen: Increased
- LDH: Increased
- B.M: Erythroid hyperplasia Normal M/E = 4\1

except Aplastic & megaloblastic

iii) Detection of the cause (specific):

a. Blood film:

- Spherocytic RBCs : Spherocytosis
- Target cells : Thalassemia

ليس في الـ Hb
 Reduced M/E

b. Osmotic fragility : Increased with spherocytosis

c. Hb electrophoresis : Thalassemia - sickle cell

d. Enzymatic assay : G6PD deficiency, Pyruvate kinase deficiency

e. Others : Sickling test - Ham's test - Coomb's test

f. Isotopic Study: Cr51 Labeled RBCs = Diagnostic test of Hypersplenism

Evidence of iv hemolysis

Haemoglobinemia, ↑ Hb in blood

- ↓ Haptoglobin & Hemopexin
- ↑ Methemalbumin - Hb + Albumin
- Hburia & Hemosiderinuria

ليس في الـ Hb
 عيالي في الدم
 ليس في الـ Hb
 ليس في الـ Hb

life span of RBC 10-15 day
formed in spleen →

Hematology

Dr/M. Allam

Treatment :

- Blood transfusion
- Treatment of the causes OR prevention of precipitating factors
- Supplementation By Folic acid & vit B₁₂
- Fe-chelating Agent
- Splenectomy In cases of Hypersplenism

H.Spherocytosis → Osmotic fragility

PNH → Flow cytometry

SCA → Hb electrophoresis

Thalassemia → Hb electrophoresis "Hb f"

G6PD → Heinz body, enzyme deficiency
PK

Autoimmune → Coombs test

hypersplenism

Hereditary or familial $\Rightarrow$ ^{Autosomal} dominant

↑↑ MCHC ← السبب ! Gall Bladder stone ← الحصى المرارية

Hereditary Spherocytosis

Definition: Autosomal dominant disease characterized by increase RBCs fragility

Pathophysiology:

- Defect in membranous lipoprotein (spectrin) Leading to loss of elasticity and plasticity (deformability) presented with extra vascular haemolysis. *may occur intra vascular in crisis*
- Effect of haemolysis (see above)

Clinical picture:

- Features of anaemia (as above)
- Features of haemolysis (as above)

Plus : Positive family history

Other rare forms of membrane

disorders :

- Elliptocytosis: Autosomal dominant (Mild form of spherocytosis)
- Stomatocytosis : defect in stomatin (as spherocytosis)

Investigations :

- Diagnosis of anemia : (as above)
- Diagnosis of hemolysis : (as above)
- Detection of the cause:

- Blood film: Spherocytic RBCs

- RBCs indices: $\downarrow$ MCV & $\uparrow$ MCHC *والتالي*

MCV - Osmotic fragility: Increased (Diagnostic)

mch $\rightarrow$ normal

Differential diagnosis: Other causes or hemolysis

Treatment:

- As any haemolytic anaemia
- Splenectomy (surgical removal or embolic) is indicated in :
 - 1- Severe anaemia (Increase frequency of BT) *Transfusion*
 - 2- Family history of deaths by Spherocytosis.

NB : Hemoglobin A1C (Glycated Hgb) $\rightarrow$ Abnormally low as life span of RBCs is decreased , thus even with overall blood sugar the A1C will be lower than expected.

Paroxysmal Nocturnal Hemoglobinuria

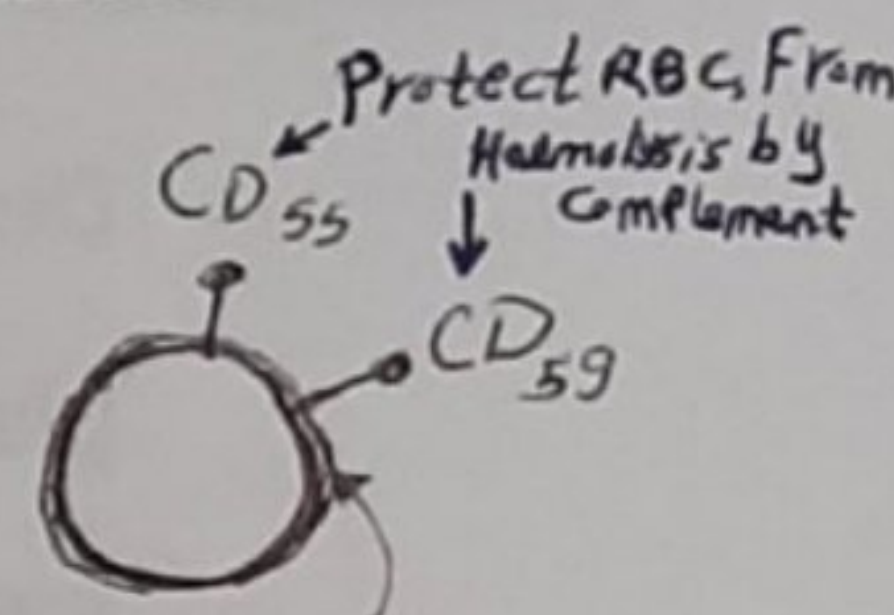
سليم الخلايا والظري متوقع (PNH) 1- Haemolytic anemia
2- aplastic anemia "pancytopenia"
3- Bleeding - thrombocytopenia
4- Thrombophilia Platelet aggregation "not helpful"

Acquired rare defect in stem cells presented with RBCs, WBCs & platelets abnormalities.

Pathophysiology :

1- RBCs:-

- RBCs defect :- Deficiency of membrane protein glycosyl phosphatidyl inositol (GPI) this defect makes the cell more susceptible to destructive effect of **C3**. **Complement**
- mainly during **sleep** (optimum **acidosis**). → activation to complement → attack RBC → intravascular Haemolysis
- This results in intravascular hemolysis (see effect of hemolysis above)



2- WBCs: PMNL dysfunction (chemotactic defect)

3- Platelets: Thrombocytopenia but sometimes aggregation activities flare up leading to thrombosis.

Clinical picture:

1- RBCs: - Features of anaemia (as above)

- Features of hemolysis (as above) mainly **intravascular**

2- WBCs: - Recurrent infection

3- Platelets: (Venous thrombosis) e.g.

Thrombophilia is more than Thrombocytopenia



- Budd chiari ^{occlusion of both hepatic veins} - Gut ischemia
- Cerebral vein thrombosis produces papilledema
- Red Painful nodules may occur in the skin.

Investigations :

1. Diagnosis of anaemia : (as above)

PLUS:

WBCs & platelets → May be Decreased (Pancytopenia)

2. Diagnosis of haemolysis : (as above) (features of intravascular haemolysis)

3. Detection of the cause:-

A- diagnostic test

- Ham's test: RBCs haemolysed by acidity (old test)
- Sucrose : RBCs haemolysed by sucrose (old test)
- Flow cytometry (Recent test) Counting CD around RBC.

Most diagnostic.

B- Bone Marrow

- As usual there is Hyperactivity , But hypoplasia or aplasia may be detected or predict neoplastic changes (leukemia)

C- Other

- Leucocytes alkaline phosphatase score: low
- The complement lysis sensitivity test:-
 1. Group I:- normal sensitivity to complement.
 2. Group II:- moderate.
 3. Group III:- marked (at dilutions of 15 to 20-fold).

Differential diagnosis:-

- Paroxysmal cold haemoglobinuria
- Other causes haemolytic Anaemia
- Ischaemic bowel disease

Treatment

- 1- Blood transfusion: must be done for Severe cases.
- 2- Steroid 25 mg on alternative day → inhibit Complement
- 3- Thrombolytics & Anticoagulants : In cases with manifest thrombosis
- 4- Bone marrow transplantation (BMT)

Hemophilia
G6PD boy 7 Year

Glucose 6 phosphate dehydrogenase deficiency

(G6PD)

Definition : X-linked enzymatic deficiency characterized by easily hemolysis due to exposure to oxadives.

Pathology :

a) G6PD involved in HMS (hexose monophosphate shunt)

- For formation of NADPH & glutathione (which are protective to RBCs membrane).
- Defect in G6PD leads to inability of the RBCs to withstand oxidative materials, so easily hemolysed (intravascular)

b) Effect of intravascular hemolysis (see above)

Clinical picture :

a) Clinical picture of anemia : Usually mild or absent.

b) Attacks of intravascular hemolysis precipitated by exposure to oxidative stress as :

- ✓ Drugs: Aspirin - Anti malaria - Sulfa - vit.k - Dapson - INH - probenecid - penicillamine - procainamide
- ✓ Favism : fava beans
- ✓ Acidosis : as DKA
- ✓ Infections.

Types of the attacks :

<u>Type A :</u>	<u>Type B :</u>
- In black Africans - <u>Mild</u> deficiency of G6PD enzyme - Occure <u>only</u> on <u>old</u> RBCs - Presented as : Healthy person with recurrent episodes of hemolysis	- In Mediterranean area - <u>Marked</u> deficiency of G6PD - Occure in old & <u>new</u> RBCs - Presented as : <u>Chronic hemolytic anemia</u> with recurrent attacks of hemolysis

Intravascular
Iron deficiency anemia
Hb 3.4 g/dl

➤ **Favism :** combined G6PD deficiency plus abnormal metabolism of fava bean to form on oxidative material (Common in Mediterranean)

Investigations

- Diagnosis of anaemia :- (as above)
- Diagnosis of hemolysis :- (as above)
- Detection of the cause:-

Blood film → Heinz bodies → oxidized Hb.

During the attack : Heinz bodies + - Features of Intravascular haemolysis.

Diagnostic features : Enzymes assay

نظراً لسبوعيه بعد ال attack والعمل
N.B : Reticulocyte has a normal G6PD level, So for accurate diagnosis , enzymatic assay during reticulocytosis must be neglected. *التليل*

Treatment

- ✚ Avoidance of oxidatives as drugs
- ✚ Treatment of infection.
- ✚ During the attack : treated as any hemolytic anemia e.g. by blood transfusion

Drugs must be avoided in cases of G6PD Deficiency

- Dapsone • Flutamide • Methylene blue • Nalidixic acid
- Nitrofurantoin • Phenazopyridine • Primaquine • Sulfacetamide
- Sulfamethoxazole • Sulfanilamide

Hemoglobinopathies include :

(A) Sickle cell anemia

(B) Thalassemias

(A) Sickle cell anaemia

Definition : Hereditary defect in globin beta chain (HBs) of rapid polymerization and precipitation (Sickling)

Pathophysiology

- Replacement of glutamic acid (amino acid number 6 on beta chain) by valine leading to formation of HbS.
- HbS polymerized and precipitates → leads to Sickling of RBCs after exposure to "hypoxia acidosis - infection - dehydration."
- Occulusion of blood vessels by the sickle-shaped RBCS (vaso-occlusive) or RBCs undergo hemolysis (hemolytic anemia)

d) Of 2 forms :

Autosomal recessive

Autosomal Co-dominant

- Hb SA Sickle cell trait (heterozygous) : Asymptomatic - Only sickled in very severe hypoxia

- Hb SS Sickle cell anemia (homozygous) : Clinically Manifested on mild hypoxia.

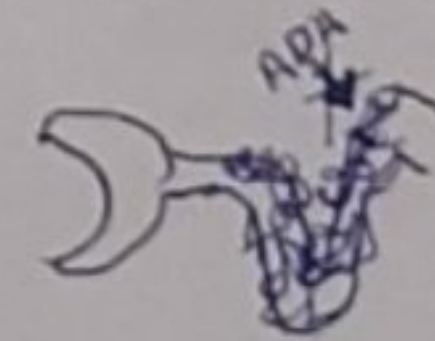
NB : HbS delivers O₂ easily to the tissues so patient of sickle cell anaemia has a less complaint

Clinical picture

- Features of anemia
- Features of hemolysis (as above)
- Vaso-occlusive → multi system affection

- Splenic artery : Auto-splenectomy (Susceptibility to capsulated organism infection)
- Mesenteric : Recurrent acute abdominal pain
- Renal : Renal infarction - nephrogenic DI insipidus
- Heart : Myocardial infarction - Haemochromatosis cardiomyopathy
- Lung : Pulmonary infarction
- Cerebral : Cerebral infarction e.g. hemiplegia
- Liver : Hepatic infarction
- Bone : Bone pain - Pathological fracture e.g. Neck of femur
- Limbs : Leg ulcers
- Penile: Priapism.

(Case) ملائقن الطحال مش حشرات



Painful aimless erection & Prolonged
Gangrene may occur.

Leukemia

Investigations

1. Diagnosis of anemia : (as above)
2. Diagnosis of hemolysis : (as above)
3. Detection of the cause :
 - Diagnostic features : - Hb electrophoresis : HbS (diagnostic)
 - Sickling test : Addition of Na Bisulphate to RBCs leads to "acidic media"
Sickling
 - Features of auto-splenectomy : - ↑ WBCs & platelets
 - Howell - Jolly bodies
 - ↓ Osmotic fragility

Treatment

➤ As any haemolytic anaemia

- Blood transfusion
- ↓ causes OR precipitating factors (Avoidance of cold exposure, infection or dehydration.)
- Folic acid Supplementation
- Iron chelating Agent

➤ Specific treatment

▪ Treatment of crisis

- Prophylaxis : - avoidance of cold exposure
- TTT of infections or dehydration
- Therapeutic : - Analgesics
- O₂ supply -
- Fluid & NaHCO₃ → Alkali
- Fresh blood transfusion or exchange

▪ Vaccination against capsulated organism.

▪ Drug increased Hb F: Azacytidine or hydroxyl urea

درم جاري
"Hydra"
دواء هيدري

▪ Bone marrow transplantation

▪ Gene therapy

MCCQ / all types of anemia have ↑ ESR except Sickle Cell anemia ↓ ESR

★ أجمل عبارة في الطب
Thalassemia + Sickle Cell anemia
موتقة شقيقة

(B) Thalassemia

Delivered from the Greek (thalassa) which means the sea

Definition :

Absent or reduced chains of globin 2 types :

- α Thalassemia : 4 loci of gene
- β Thalassemia : On chromosome 11 of 2, globin alleles

α Thalassemia

1 Locus	2 Loci	3 Loci	4 Loci
- Silent carrier - Sub clinical thalassemia	- α- Thalassemia <u>trait</u> - Mild anemia - low RBCs indices - (Microcytic hypochromic)	- α- Thalassemia <u>intermedia</u> - Hb H disease - Unstable Hb H - Mild to moderate severe anemia - Splenomegaly (early) - <u>Jaundice</u> - Abnormal RBCs indices. - Full C/P	- α- Thalassemia <u>major</u> - Severe form of homozygous thalassemia - Incompatible with life - Hydrops fetalis (treated with intrauterine blood transfusion).

β Thalassemia

1 Allele affected (Heterozygote)	Both alleles affected (Homozygote)	Thalassemia Intermedia
- β-Thalassemia <u>trait</u> or <u>minor</u> - No symptoms - Low RBC indices (Microcytic hypochromic) - Electrophoresis - <u>abnormal Hb</u> (diagnostic) - No treatment	- Thalassemia <u>major</u> (Cooley anemia) - Full C/P - Transfusion-dependent anemia.	severity does not require regular blood transfusions

* ↓ β chain → ↑ α chain → accumulate on surface → ↓ affinity to oxygen

Hematology

Microcytic hypochromic

HbF Inta 116 g/L
uterine life 21st 6 months of life
Dr/M. Allam

Thalassemia Major

Cooley's anemia - Mediterranean anemia

Definition:

Defect in globin chains synthesis characterized by formation of abnormal or unusual Hb which is rapidly haemolyzed by the spleen.

Pathophysiology

- defect in Hb : Homozygotic defect in β -chain leading to marked reduction of Hb A and increased **HbA2 & Hb F**
- Hb F is Characterized by : - Has a **high O2 affinity** (tissue hypoxia)
- **Hemolyzed by the spleen**
- Effect of hemolysis (see above)

Clinical picture

- Age of onset : After the age of **6 months**
- "during the inter-uterine life Hb F was the main type of Hb in the fetal blood, then gradually replaced by Hb A within the first 6 months of life by maturation of gamma chain to B chain"
- C/P as any **hemolytic anemia**

$\gamma \rightarrow \beta$

Investigations

- Diagnosis of **anemia** :- (as above)
- Diagnosis of **hemolysis** :- (as above)
- Detection of the cause:-
 - **Diagnostic features** :
 - Hb electrophoresis:- **Hb F (diagnostic)**
 - Hb F : Increased (20 - 90 %)
 - Hb A2 : Increased (20 - 90 %)
 - Hb A : Reduced.
 - **Specific features** :
 - Microcytic hypochromic
 - **Target cells** Diagnostic features
 - Anisocytosis & Poikilocytosis
 - **Radiological (X-ray)** : (Result from expansion of marrow spaces)
 - ✓ **Skull**: **Hair-on-end appearance**
 - ✓ **Long bone**: **Wide medulla & thin cortex**

hair
moZaic appearance

Differential Diagnosis: Other causes of hemolysis plus

- 1- Fe deficiency:- Fe and ferritin are low while iron binding capacity is high.
- 2- Acute leukaemia:- may require bone marrow aspiration
- 3- Rhesus incompatibility:- Hb electrophoresis is required
- 4- Diamond Blackfan syndrome.

Treatment**a. As any hemolytic anemia (triad)**

- Blood transfusion (Maintain Hb > 10 gm%)
- Supplementation by folic acid
- Fe chelating agent : Desferroxamine by SC pump - Recently oral forms

b. Specific treatment:-

- Splenectomy : If hypersplenism was diagnosed either by increased frequency of B.T or ⁵¹Cr
- labeled RBCs
 - Hypersplenism
 - Pancytopenia
 - Reticulocytosis
- Bone marrow transplantation & Gene therapy

Blood Transfusion

NB ⇒ IMMUNOLOGICAL HEMOLYTIC ANEMIA**➤ Alloimmune**

- ABO incompatibility
- Rh incompatibility

➤ Autoimmune

- Warm Antibody
- Cold Antibody
- Mixed type
- Drug induced

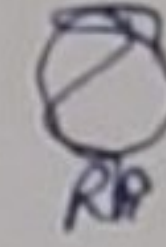
سوال نظري متوقع في الامتحان

Autoimmune hemolytic Anemia

Destruction of the RBCs under effect of Autoantibodies or complement activities.

Classification and causes

1- Warm antibody autoimmune hemolytic anemia *IgG*



➤ Idiopathic

- Collagenosis

- SLE *الذئبة*

Evans' syndrome (antiplatelet Abs and haemolytic anaemia) *"Auto immune thrombocytopenia Auto immune haemolytic anemia"*

➤ *2ry (3Ls)* : Leukaemia , Lymphoma & L-dopa

2 - Cold antibody autoimmune hemolytic anemia *IgM / IgG*

a. Chronic idiopathic (rare) called (Idiopathic cold hemagglutinin syndrome)

b. Viral infections : Measles , mumps , influenza , adenovirus , chickenpox , cytomegalovirus and Epstein-Barr virus (Paroxysmal cold Hburia)

c. Bacterial infections: - Syphilis, H. influenzae and Mycoplasma pneumoniae.

d. Some vaccinations.

3 - Mixed-type autoimmune hemolytic anemia

4 - Drug induced autoimmune hemolytic anemia

Pathophysiology (steps of hemolysis)

Warm (IgG) *الساخن* *phagocytosis*

⇒ The IgG antibodies attach to a RBCs followed by FC portion recognized monocytes and macrophages in the spleen.

⇒ These cells -will pick off portions of the red cell membrane (taking a bite)

⇒ The RBCs become spherocytes (easily-destruction in the red pulp of the spleen) so

➔ splenomegaly often seen.

Cold (IgG-IgM) *البارد* : Two types according to the formed antibodies :

➤ **IgG (Paroxysmal cold Hburia)** *نوبات صرع PNH* : - In cold antibody intravascular hemolysis was produced after exposure to cold by an IgG autoantibody leading to Hburia.

➤ **IgM (Cold hemagglutinin syndrome)** *Idiopathic* : - First vascular occlusion then hemolysis which may be intravascular or extravascular .

NB : When IgM binds to RBC at cold temperature, classical pathway of complement system is activated resulting in formation of membrane attack complex (MAC) causing intravascular hemolysis. If MAC is not formed, opsonization by C3b leads to extravascular hemolysis by spleen).

Clinical picture:-

1- WARM ANTIBODY (EXTRA VASCULAR HAEMOLYSIS MAINLY)

Definition : An auto-antibody attacks the RBCs at normal body temperature

C/P : - Patient: More in middle age female

- C/P of Hemolytic anemia
- Splenomegaly
- $\pm$ ITP (Evan's syndrome) SLE.

Lab : - Spherocytic cells & Elevated serum Ig G

2- COLD ANTIBODY (INTRAVASCULAR HAEMOLYSIS MAINLY) (Paroxysmal cold Hburia)

Definition: An auto antibody attacks the RBCs after exposure to cold

C/P : - Patient- related to the causes.

- C/P of haemolytic anaemia (acute after exposure to cold)
- Attack of Hburia with viral infection by measles, mumps or V-Z, so called Cold induced Hburia.
- $\pm$ Raynoud's phenomenon

3- MIXED FORM : - clinical picture of both types

Investigations :

- As hemolytic anemia **PLUS** +Ve Coomb's test

COOMBS TEST:

- Diagnostic test for auto immune hemolytic anemia
- used for detection of auto antibodies in the patient's serum either directly or indirectly

Direct : - Detects RBCs coated with Abs

- Method : Patient's RBCs (coated with Abs) + Coomb's antiserum

Indirect : - Detects free S. antibodies

- RBCs (gp O) + Pt. serum + Coomb's antiserum

evan's synd. - ① Auto immune Hemolytic anemia
 ② " " Thrombocytopenia
 Dr/M Allam

Treatment

1. As any hemolytic anemia
2. Treatment of the cause if possible.
3. Immunosuppressive drugs:-, steroid - Azathioprine.
4. IV immunoglobulin G : - transient response " normal immunoglobulins
5. Splenectomy (in hypersplenism)
6. Avoid exposure to cold

Drug induced Autoimmune hemolytic Anemia

- Real autoimmune : Antibody was formed and directed against RBCs e.g. methyl dopa.
- Hapten type : the drug attached to the RBCs to become, antigenic e.g. penicillin, digoxin, quinine. ^{Ex: 8:10}
- Innocent reaction : the drug attached to the RBCs to stimulate the complement e.g. Sulfa, Quinidine. ^{Ex: 8:10}

Mechanical hemolytic Anemia

- March Hemoglobinuria : RBCs destroyed by foot capillaries.
- Prosthetic - calcified valve
- Microangiopathic : - DIC - Scleroderma - Severe hypertension
 - Hemolytic uremic syndrome (microangiopathy caused by infection leading to hemolysis , hemoglobinuria & ARF)

NB : Drug induced hemolysis

1. Direct effect : Amphoterricin
2. Oxidative in G6PD deficiency (see above)
3. Immune reaction (see above)

• Auto immune

NB. Schistocytes (fragmented RBCs) : suggesting thrombotic thrombocytopenic purpura , hemolytic uremic syndrome or mechanical damage.

NB. Thrombocytopenia and autoimmune hemolytic anemia :

- SLE (Evan's syndrome)
- CLL
- Microangiopathic hemolytic anemia

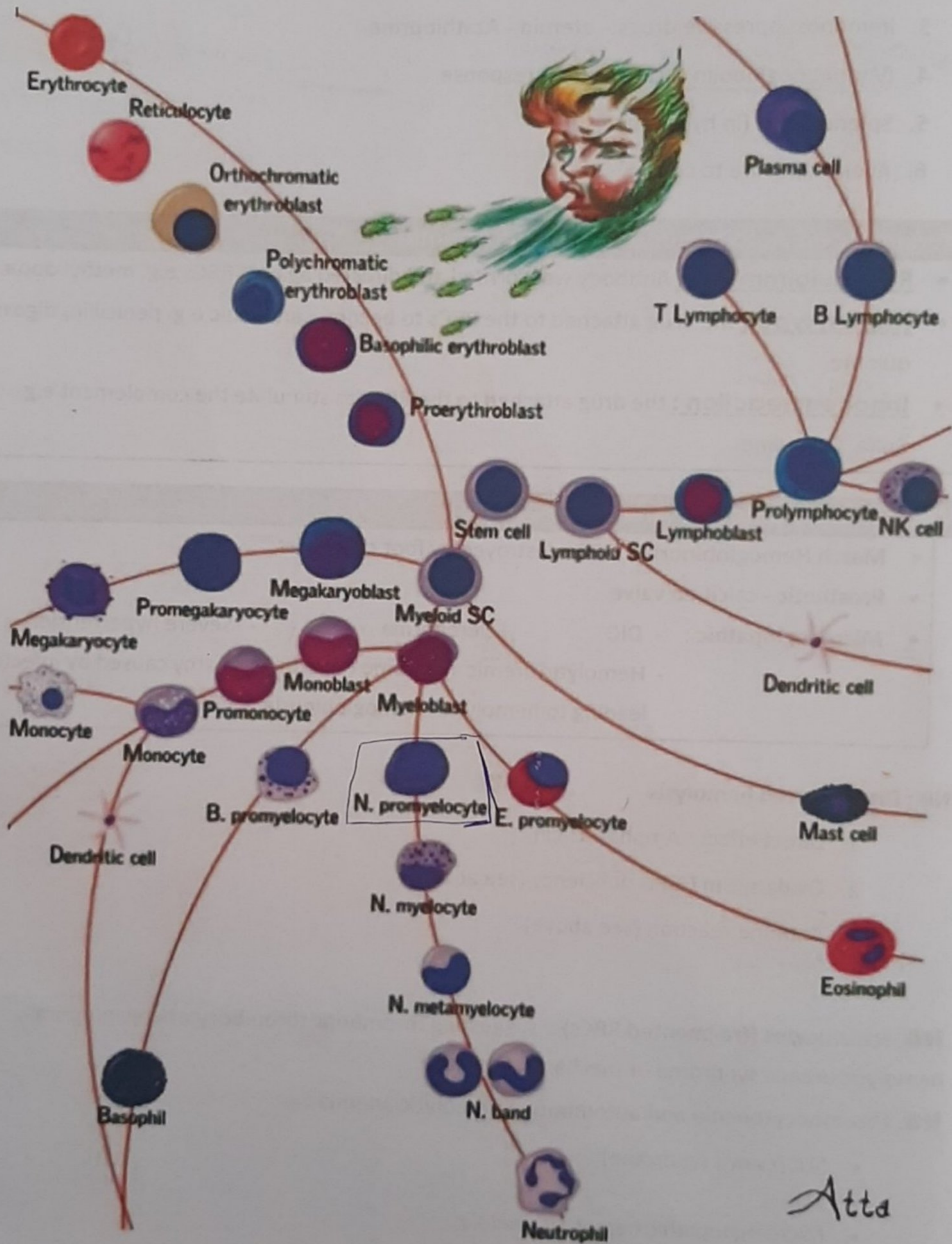
Hematology
Special Invest 100 C 100

- Thrombophilia
- neutropenia

★ diff. diagnosis of Generalized lymphadenopathy and discuss
Dr/M. Allam one of them

[illegible]

You must remember this diagram before WBCs disorders. See page 5



Disorders of Leukocytic Count

Agranulocytosis

= neutropenia

Neutrophils = 45 - 70% = (3000-7000 cells/mm³)

Def : reduction in the number of WBCs as may be dangerous as "granulocytopenia"

Classification

- **Neutropenia** : absolute neutrophil counts <1500/mm³
- **Severe neutropenia** : absolute neutrophil counts <500/ mm³
- **Agranulocytosis** : absolute neutrophil counts <100/mm³

Aetiology

1. **Hereditary**: cyclic neutropenia
2. **Acquired**:
 - **Infection**: viral or severe bacterial
 - **Immunological**
 - **Pancytopenia**
 - **Drug-induced**:

Drug induced neutropenia

- **Antiepileptics**
- **Antithyroid** : carbimazole and methimazole
- **Antibiotics** : penicillin, chloramphenicol and co- trimoxazole
- **Antidepressant** : mirtazapine
- **Antipsychotics** : atypical as clozapine.
- **Cytotoxic drugs or gold**
- **NSAIDs** : indomethacin, naproxen, phenylbutazone

Clinical picture

- May be **Asymptomatic**
- May presented with **sudden fever**, rigors and **sore throat**.
- Infection of any organ may be **rapidly progressive**. (e.g.; pneumonia, UTI).
- Septicemia may also **progress rapidly**.

Investigations

- **CBC** : Neutrophil **less than 500** cells/mm³.
- **BM**: **normocellular** with **pro-myelocyte maturation arrest**.

Differential diagnosis

- **aplastic anemia**
- **myelodysplasia**
- **paroxysmal nocturnal hemoglobinuria**
- **leukemias**.

Treatment:

→ Asymptomatic patient:-

- ✓ monitoring with serial blood counts,
- ✓ withdrawal of the cause
- ✓ general advice on the significance of fever.

→ tit of Infection:-

broad-spectrum penicillin or cephalosporin (piperacillin tazobactam, ceftazidime or ticarcillin clavulanate) or meropenem in combination with gentamycin or amikacin.

→ Resistant cases (fever more than 4-5 days):-

Antibiotics must be changed to a glycopeptide (e.g. vancomycin), and subsequently an antifungal agent (e.g. amphotericin B) is added to the regimen.

→ Recombinant G-CSF (filgrastim)

جوا انساي
بيستحق نفس معزز
immulant
G-CSF

NB: Transfusion of granulocytes would have been absolution to the problem. However, granulocytes live only ~10 hours in the circulation (for days in-spleen or other tissue), which gives a very short-lasting effect. In addition, there are many complications of such a procedure.

Neutrophilia

increase neutrophil > 7000

A- Normally responding bone marrow to

1. **Infection**
2. **Inflammation:** tissue necrosis, infarction, burns, arthritis
3. **Stress:** overexertion, seizures, anxiety, anesthesia
4. **Drugs:** lithium, beta agonists
5. **Splenectomy**
6. **Hemolytic anemia** **Leukemoid** malignancy

B- **Abnormal bone marrow**:- Myeloproliferative disorders (Leukaemia)

Basophils 0-2% (0-100 cells/mm³)

Basophilia

- **Infections** : viral infections (varicella), chronic sinusitis
- **Inflammatory** : inflammatory bowel disease, chronic airway inflammation, chronic dermatitis
- **Myeloproliferative** : Leukemia, polycythemia vera, myelofibrosis
- **Endocrinal causes** : hypothyroidism, ovulation, estrogens

Basopenia

- ✓ Endocrinal: hyperthyroidism, cushing
- ✓ Steroid therapy
- ✓ Pregnancy.

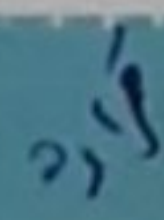
Eosinophils (2-4% = 40-400 cells/mm³)

Eosinophilia

- 1) **Parasitic infestations**; Ascaris, Hookworm, Strongyloides, Loafler's S
- 2) **Allergic disorders**: Hay fever, Other hypersensitivity reactions, including drug reactions
- 3) **Skin disorders**:- Urticaria, Eczema
- 4) **Pulmonary disorders**:- Bronchial asthma, Tropical pulmonary eosinophilia, Allergic bronchopulmonary aspergillosis or Churg-Strauss syndrome
- 5) **Malignant disorders**: Hodgkin's lymphoma, Eosinophilic leukaemia
- 6) **Miscellaneous**: Hypereosinophilic syndrome, Sarcoidosis, .
- 7) Eosinophilic gastroenteritis

Eosinopenia

- ✓ Endocrinal: Gushing - Steroids
- ✓ Pregnancy
- ✓ Pyogenic infection.



Lymphocytosis

Cellular immunity

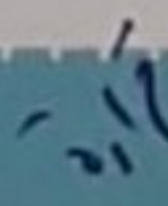
Lymphocytes : 25 - 40% (1700 - 3400)

Absolute lymphocytosis (lymphocytic count elevated)

- Acute infections: CMV, Pertussis, hepatitis *viral & TB*
- Chronic infections: tuberculosis
- Lymphoid malignancies: CLL, lymphoma.

Relative lymphocytosis

- ✓ higher proportion (>40%) of lymphocytes, while the absolute lymphocyte count (ALC) is normal (less than 4000)
- ✓ Normal in children less than **2 years**
- ✓ Acute phase of several **viral** illnesses
- ✓ **Connective** tissue diseases
- ✓ **Endocrinal** causes: Thyrotoxicosis & Addison's disease



Lymphopenia

- Acute infections
- Steroid therapy
- Malnutrition or malabsorption
- Endocrinal: Cushing
- Immunodeficiency S
- Hypersplism



Monocytosis

Monocytes 4 - 8%% (400-800)

- **Infections:** tuberculosis, brucellosis
- **Blood malignancies:** chronic monocytic leukemia - lymphoma
- **C.T diseases:-** SLE , IBDs or sarcoidosis.
-

Leukemia

WBCs neoplasm.

Definition :

Very rapid proliferation either for immature cells (blast) or mature cells (cyte) within the BM followed by Dissemination and multi organ infiltration.

acute *chronic*

Aetiology: (Theories..)

a) **Genetic:** Supported by the following evidences

- High incidence in identical twins
- High incidence in congenital disorders as Down's syndrome
- Presence of Philadelphia chromosome in CML

b) **Environment:**

- Exposure to radiation
- Chemicals as Benzene
- Toxins & Drugs : Alkylating agent

c) **Infection:** Mainly by EB or retrovirus (HLVI & II)

Ebstein Barr

Human lymphotropic virus

Classification of leukemia

Acute Leukemia	Chronic Leukemia
▪ Rapid onset ▪ Highly progressive course	▪ Slower course ▪ May show blastic crisis
• Acute lymphocytic L. (ALL) <i>حادة</i> • Acute Myeloid L. (AML) <i>non lymphocytic</i>	• Chronic lymphocytic L. (CLL) <i>كروني</i> • Chronic Myeloid L. (CML) <i>non lymphocytic</i>

Clinical presentation of leukemia depends on 3 stepped stages.

- B.M. proliferation :
For production of WBCs, so there is a reduction in RBCs & platelets formation.
- Abnormal WBCs Either of no function or incorrectly functioning.
- Multi organ infiltration as (liver, spleen, CNS, L.N.,)

Acute Leukemia

Malignant proliferation occurring in an early hematopoietic precursors of WBCs "Blast cells". Which fail to differentiate into mature WBCs but continue to proliferate in an uncontrolled fashion.

It has two main types .

☠ Acute lymphoblastic leukemia "ALL"

- Common in Children (90%)
- Sub-differentiation to B. cell & T. cell types
- T cell in ALL is highly malignant

☠ Acute myeloblastic leukemia "AML"

- Common in Adults
- Arises from multi potent stem cells, so it may be granuloblast, erythroblast, macrophage or megakaryocytic cells

Clinical picture

1) BM failure & replacement manifested by :

- RBCs** : Anemia (as usual) normocytic normochromic
- platelets** : - bleeding "Epistaxis, bleeding gum & S.C. bleeding ,....etc. "
 - it may be fatal as in cerebral hemorrhage.
- WBCs** : Recurrent infections

Fever + Sore throat, Stomatitis, mouth ulcer ± cervical lymphadenopathy.

OR Severe & serious forms as pneumonia & UTI

The commonest organisms are gram-negative bacteria (E coli, Klebsiella, Pseudomonas) or fungi (Candida, Aspergillus).

Manifestation of tissue affection :

1- Reticulo-endothelial system (RES)

✓ Lymphadenopathy (mainly with ALL)

- Small, symmetrical, discrete, not tender or painful
- External: as cervical, mediastinal, inguinal, porta-hepatis, Axillary
- Internal: presented with Mediastinal syndrome, obstructive jaundice or abdominal masses

✓ Hepatosplenomegaly

✓ Bone marrow infiltration : bone pain and tender sternum = leukemia

Leukemia may cause Tissue infiltration, infarction or infection

2- Nervous system :

- Meninges : Increased ICT or cord compression
- Hemispheres : focal neurological deficit according to the site
- Retina : visual defects
- Brain stem : cranial nerves palsy

3- Lung

- Parenchymatous : Infection or hemoptysis
- Pleura : Haemorrhagic effusion
- Mediastinum : mediastinal syndrome ~ Pressure manifestation.

4- Heart :- cardiomyopathy ~ restrictive Rt side & haemorrhagic Pericardium effusion may occur.

5- Abdominal:-

- Organs infiltration : Hepatosplenomegaly
- Intestinal : Diarrhoea + dysentery
- Peritoneal infiltration : Pain and haemorrhagic ascites
- Porta hepatis or pancreas : Obstructive jaundice
- Kidney : Urate crystal (less gouty) & Renal failure (infiltration)

6- Skin :

~ low immunity.

- Pruritus (leukaemia cutis) d.t.o Release of histamine from degranulated Basophils

- Chloroma (mainly facia) with pigmentation Solid skin lesion
Collection of leukemic cells in skin forming solid mass

7- Leukostasis :-

- due to Hyper-viscosity leading to hypo-perfusion and vascular occlusion
- manifested by pain, ischemia of (brain, bone or lung) & priapism.

8- Manifestations of metabolic changes :-

- Loss of body weight and asthenia.

↑ purine base

- Hyper-uracemia

↑ destruction of WBC → ↑ Purine base

Release of Tumor necrosis factor
↑ Purine base → ↑ uric acid

- Hypo-natraemia & hypokalaemia

9- Gum hypertrophy

DD - familial

- leukemia

- Thalassemia

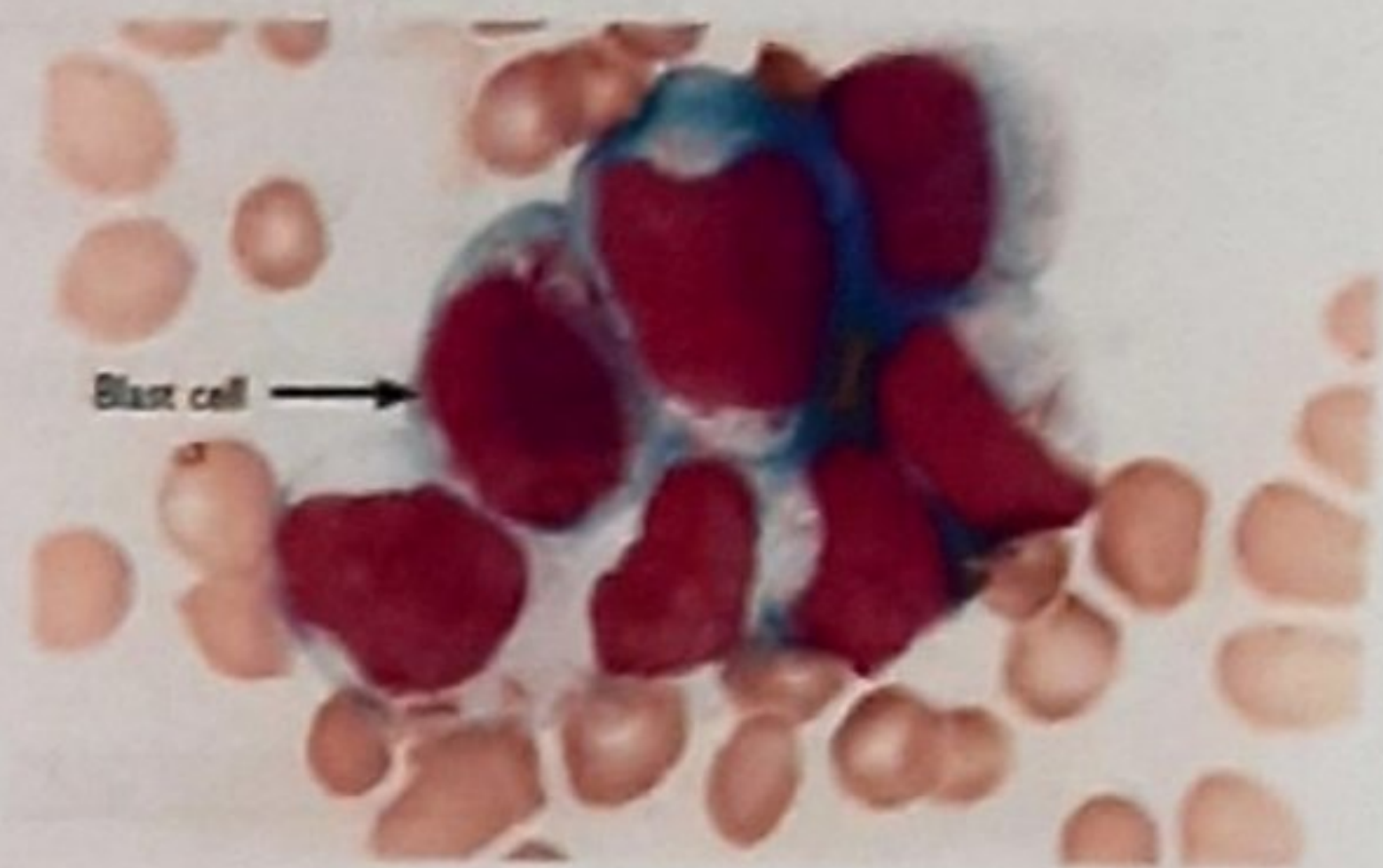
- Drugs → Phentoin ~ anti-epileptic, anti-arrhythmic
Ca channel Blocker



Investigations:-

CBC :

- **RBCs:** Normochromic Normocytic anaemia
- **Platelets:** Thrombocytopenia
- **WBCs:**
 - TLC increased (as $20-50 \times 10^3 / \text{mm}^3$)
 - Blast cells increased (as 30-90 %) diagnostic.
acute leukemia
 - For differentiation of the type :- Peroxidase positive in AML



Peripheral Blood Film

ESR: Markedly elevated

BM: (diagnostic) Excess blast cells > 30%

Cellular differentiation: By immimological - chemical - flow cytometry

Others :

- a. Serum uric acid : elevated
- b. LDH : elevated
- c. Serum Electrolytes : as Na & K *decreased*
- d. X-ray bone : osteopenia
- e. CSF & CT brain.
- f. Liver & kidney functions.

differentiation bet. AML & ALL

- AML shows Auer rods in the cytoplasm of blasts
- Sudan black stain is +ve in AML & -ve in ALL.
- Deaminase in ALL , Muramidase enzyme in AML.

Differential diagnosis:-

- a. Causes of **anemia** & **thrombocytopenia**
- b. Causes of fever and **sore** throat
- c. Causes of fever and **lymphadenopathy**
- d. Causes of **leucocytosis** (leukmoid reaction).

Sub-leukaemic leukaemia

- TLC is normal or subnormal with > excessive blast cells in *Peripheral Blood Film*

Aleukaemic leukaemia

- TLC is normal > blast cells are normal or subnormal > diagnosis depends on BM.

الكلية ونقو لها Clinical Picture

FRENCH - AMERICAN - BRITISH (FAB) CLASSIFICATION OF AML :

- ✓ M0 : Undifferentiated leukemia.
- ✓ M1 : Myeloblastic leukemia without maturation.
- ✓ M2 : Myeloblastic leukemia with maturation.
- ✓ M3 : Promyelocytic leukemia.
- ✓ M4 : Myelomonocytic leukemia.
- ✓ M5 : Monocytic leukemia.
- ✓ M6 : Erythroleukemia : red blood cell precursors & myeloid blasts.
- ✓ M7 : Megakaryoblastic leukemia : the worst prognosis.

FRENCH - AMERICAN BRITISH (FAB) CLASSIFICATION OF ALL

- ✓ L1 : small homogenous cells
- ✓ L2 : large heterogenous cells
- ✓ L3 : large aggressive burkitt like cells .

Chronic Myeloid Leukaemia

Myeloproliferative disorder characterized by predominant proliferation of granulocytic cells

Usually affects middle age and equal in both sex

Clinical picture :-

Clinical picture of gradual onset and slowly progressive course.

May be Asymptomatic & discovered Accidentally

Begins with splenomegaly & constitutional manifestations as (fever , Wt loss)

a) Manifestations of BM failure: Anemia , bleeding and infections(As above).

b) Manifestation of tissue infiltration

1- Reticulo-endothelial system (RES)

- **Splenomegaly :** *Huge* 
 - May presented : with left hypochondrial pain or dyspepsia. *"Almighty signs"*
 - Local/Ex : may show huge spleen, multi-notched, pitting + splenic rub.
- **lymphadenopathy** (Moderate and not common)
- **Hepatomegaly**

2- **Nervous system** : as Acute leukemia but rare

3- **Lung** : infection & infiltration " dyspnea & hemoptysis " as above

4- **Heart** : cardiomyopathy & heart failure.

5- **kidney** : pyelonephritis , Renal failure (infiltration) OR Ureat crystal

6- **Skin** : Pruritus , Chlosoma , pigmentation.....(as above)

7- **Thrombosis and leukostasis** : caused by hyper-viscosity and thrombocytosis

8- **Manifestations of metabolic changes** : as above

9- **Genital** : testicular infiltration , failure & painful priapism.

10- **Gum hypertrophy**

➤ **Blastic crises** : acute shift to blastic form may occure . (clinically as AML).

Investigations

CBC:

- **RBCs:** Normochromic normocytic anaemia
- **Platelets:** Early Thrombocytosis then Thrombocytopenia
- **TLC:**
 - Increased (more than 100,000 cell/ml)
 - Blast cells low (except during blast crises) Myelocytes the most dominant
 - Peroxidase positive + leukocyte alkaline phosphatase are elevated

myelocytes

ESR: markedly elevated

M/E = 2/3

Philadelphia chromosome

BM: - Hypercellular with excess myelocytes

- elevation of M/E ratio as high as 50 (myeloid/Erythroid ratio normally 2-3)

Philadelphia chromosome: Detection (diagnostic)

- Philadelphia chromosome is abnormal chromosomal changes characterized by translocation of chromosome 22 long arm to chromosome 9
- it carries a good prognosis

From TrkA To Met3b

+ trkA → met3b
22 → 9

Others:

- ↑ LDH & Serum uric acid
- Serum Electrolytes : Na & K.

Blood Smear
 ↓
 CBC
 Platelet
 WBC

Chronic lymphoid leukemia

لا يطيق
 low grade malignancy

Myeloproliferative disorder characterized by predominant proliferation of lymphocytic cells

Clinical picture

- Usually affects old age
- Of gradual onset and slowly progressive course.
- Asymptomatic (25% of cases) : Accidentally discovered by lab.
- Manifestations of BM failure : Anemia , bleeding , infections , As above
- Manifestation of tissue infiltration :
 - I. Reticulo-endothelial system (RES) :
 - lymphadenopathy / (common) : May be very large LN, usually painless, generalized, affecting external and internal LN (see above)
 - Hepatosplenomegaly
 - II. Others : CNS , CVS , lung , urinary , genital as above
 - III. Skin : (common) as above Chloroma
- Immunological dysfunction (characteristic) : as
 - Decreased gamma globulin or monoclonal gammopathy,
 - Autoimmune Hemolysis , Autoimmune thrombocytopenia or recurrent infection.

Investigations

Worm

التهاب الكبد الوبائي B
 B.M. infiltration

Auto immune Hemolysis
 Auto thrombocytopenia

CBC :

خفيف

Auto immune Hemolysis

- ✓ RBCs : Normochromic normocytic anemia + Spherocytic with evidence of hemolysis (+ve coomb's)
- ✓ Platelets : Thrombocytopenia
- ✓ TLC : - Increased (as $50-250 \times 10^3/\text{mm}$)
 - Blast cells low + ruptured leukocyte (basket cell)
 - lymphocytes the most dominant (may be absolute)

ESR : Markedly elevated

BM : Infiltrated with lymphocytes

Others : Serum uric acid - LDH = elevated

Immunological assessment :- As Ig type and level.

Treatment of leukemia

A) Supportive tt :

- Anemia : Packed RBCs transfusion
- Bleeding : Platelets transfusion *Prophylactic antibiotic + Isolation*
- Infection : Antimicrobial or vaccination
- Leukostasis : Leukophoresis
- Immunotherapy : BCG - Levemizol - Monoclonal AB - Desensetization
- Post treatment electrolytic shooting (ATLS: acute tumour lysis syndrome) *يشرب بـ لتر مياه على الأقل في اليوم*

B) Specific therapy for each type :

Important definitions

A Induction phase : Initial intensified therapy for early remission and a lower risk of disease resistance.

B Consolidation and maintenance:-

- Treatments are intended to prevent disease recurrence.
- ① → Consolidation is a repetition of induction chemotherapy with additional drugs.
- ② - Maintenance lower doses of induction phase.

عالم نفع نسبي

Acute lymphoblastic leukemia (ALL)

A- Induction (1st month)

For adults :

- Prednisone^{lo} , Vincristine. *oncovine* *مبارك*
- Anthracycline Drugs other drugs (L-asparaginase or cyclophosphamide)

For children : consists of three drugs

- Prednisone, L-asparaginase, and vincristine

B- Consolidation

Adults (1-3 months) children (4-8 months)

Aim : To eliminate any remaining leukemic cells

Low to average risk ALL : methotrexate and 6-mercaptopurine

High risk ALL : Higher drug doses of these drugs plus additional drugs.

C- Maintenance (2 years)

- Aim : To prevent disease recurrence once remission has been achieved.
- drugs : Lower doses of methotrexate and 6-mercaptopurine (6-MP)
- Alternatively for high-risk or relapsed patients BMT

Acute myeloid leukemia (AML)

- Treatments vary some what according to the age of the patient and according to the specific subtype of AML.
- But may be treated as ALL without CNS prophylaxis

Chronic lymphocytic leukemia (CLL)

- ✓ A large group of CLL patients have low-grade disease, which does not benefit from ttt.

Indications of treatment

- Falling hemoglobin or platelet count
- Progression to a later stage of disease
- Painful, disease-related overgrowth of lymph nodes or spleen
- An increase in the rate of lymphocyte production

Treatment "Combination"

Chemotherapy : chlorambucil or cyclophosphamide. plus

Corticosteroid : prednisone or prednisolone.

The use of a corticosteroid has the additional benefit of suppressing some related autoimmune diseases, such as immunohemolytic anemia or immune-mediated thrombocytopenia.

In Resistant cases:-

Single-agent treatments with nucleoside drugs such as **fiudarabine** , **pentostatin**, or **cladribine** may be successful.

In young patient : BMT may be considered

Chronic myeloid leukemia (CML)

Defined As chronic manageable condition

1- Drugs

- Busulphan (myleran)
- Imatinib (Gleevec) therapy
- blastic crisis must be treated as AML

Donor (p)

2- Allogeneic bone marrow transplantation

- Indications

- More advanced
- Uncontrolled state
- Intolerance to imatinib
- If the patient wishes to attempt a permanent cure

- Technique

Firstly high-dose chemotherapy and radiation followed by infusion of bone marrow from a compatible donor.

- Results

Approximately 30% of patients die from this procedure.

Hairy cell leukemia (HCL)

Indications of treatment:

- Low blood cell counts
- Frequent infections
- Unexplained bruises or anemia.

DRUGS

- Cladribine : for 1 week daily IV or single-so injection
- Alternatives :
 - Pentostatin : IV / 4 weeks for 6 months
 - Rituximab infusion
 - Interferon-alpha.

Hodgkin's lymphoma

Definition: Hodgkin's lymphoma is characterized clinically by the orderly spread of disease from one lymph node group to another and by the development of systemic symptoms with advanced disease.

Pathologically: The disease is characterized by the presence of Reed-Sternberg cells.

Clinical picture

Patients with Hodgkin's lymphoma may present with the following:

A) Systemic: about one-third (Vs) of patients

1. Low-grade fever
2. Night sweat
3. unexplained weight loss of at least 10% of the patient's BW
4. Pruritus: due to increased levels of eosinophils
5. Fatigue
6. Cyclical fever: patients may also present with a cyclical high-grade fever known as the **Pel-Ebstein** fever.

NB: Systemic symptoms such as fever, night sweats and weight loss are known as B symptoms

B) Nodular

Exogenous LN

- ✓ **Lymph nodes:** painless, rubbery and discrete; may form satellite arrangement.
- ✓ **cervical** and **supraclavicular** are most frequently involved
- ✓ **Pain** following **alcohol** consumption

Endogenous LN

- ✓ As retroperitoneal, mediastinal or LN in porta hepatis.

C) Extra-nodular

- i. **Splenomegaly:** occurs in about 30%.
- ii. **Hepatomegaly:** present in about 5% of cases.
- iii. **Skeletal invasion** presented with back pain
- iv. **Peritoneal** infiltration may presented with ascites

- v. **Lung** :-infiltration of lung or pleura
- vi. **Neurological** infiltration pressure effect according to the affected site.
- vii. **Skin** presented with itching and or pigmentation.

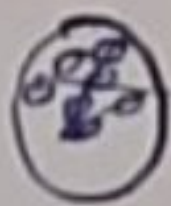
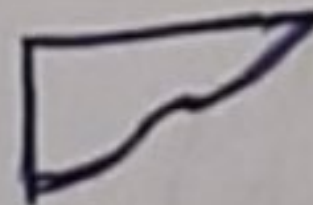
Staging of HL *clinical picture*

The Ann Arbor staging classification

Stage I	Single lymph node region
Stage II	Two or more lymph node regions on the same side of the diaphragm
Stage III	Involvement of lymph node regions on both sides of the diaphragm
Stage IV	Disseminated involvement of one or more extralymphatic organs.

- If the **Spleen** was enlarged the symbol **S** must be added as (III_s)
- The **Absence** of systemic symptoms is signified by adding **A** to the stage.
- The **Presence** of systemic symptoms is signified by adding **B** to the stage.

Prognosis: The adverse prognostic factors: "Criteria of Bad Prognosis"

1. Age > 45 years
2. Stage IV disease
3. Hemoglobin < 10.5 g/dl
4. Lymphocyte < 600- (or 8%) 
5. Male
6. Albumin < 4.0 g/dl 
7. White blood count > 15,000

Investigations

A) Blood tests :

Toxins of Tumour

- RBCs : anaemia (BM suppression, infiltration, autoimmune or hypersplenism)
- WBCs : granulocytosis with relative lymphocytosis or eosinophilia
- Platelets : may be normal or reduced
- ESR : elevated

- ESR marked elevated in T.B., collagen diseases, malignancy
ESR > 100

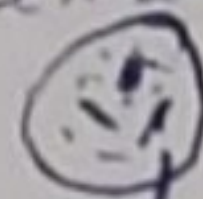
Stages of LN Biopsy

Hematology

I Lymphocytic Predominant



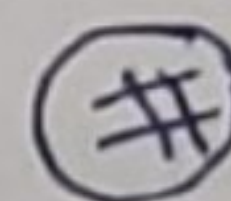
II Mixed Cellularity



III Nodular Sclerosis



IV Lymphocytic depletion



B) Lymph node biopsy

"Mandatory"

Macroscopy : LNs are enlarged, but their shape is preserved because the capsule is not invaded.

Microscopy:-

Complete or partial distortion of the lymph node architecture by:-

- Scattered large malignant cells known as Reed-Sternberg cells (Typical & Variant)
- Infiltration by lymphocytes, histiocytes, eosinophils and/or plasma cells.

The typical

- 1- **Large size** (20-50 micrometres), **abundant**, granular/homogeneous cytoplasm
- 2- **two mirror-image nuclei** (owl eyes) each with an eosinophilic nucleolus and a thick nuclear membrane (chromatin is distributed at the cell periphery).
- 3- In about **50%** of cases, the RS cells are infected by **EBV**

Further Reading

The Variants:

Hodgkin's cell : atypical mononuclear RSC IS Lacunar & large, with a single hyperlobated nucleus / Pleomorphic RSC has multiple irregular nuclei.

C) Positron emission tomography (PET)

Screening for any malignancy

D) Gallium Scan may be used instead of a PET scan.

For screening

Treatment

❖ Symptomatic treatment:-

- Anti-pyretic for fever
- Control of anaemia

❖ Specific treatment:

"Radiotherapy & chemotherapy"

1. Early stage (I-A or II-A): radiation therapy or chemotherapy.
2. Later disease (IV-A or IV-B): Combination chemotherapy alone.
3. Any stage, with a large mass in the chest: combined chemotherapy and radiation therapy.

Chemotherapy regimen (ABVD)

- ✓ Adriamycin, bleomycin, vinblastine and dacarbazine.
- ✓ Treatment typically takes between **six** and **eight** months, but longer treatments may be required.

❖ Surgical removal of LN : for releasing of pressure effect.

Non-Hodgkin's lymphoma

Def: This includes all lymphomas without Reed-Sternberg cells.

Incidence:

- ✓ Age: old age (65 - 70 y)
- ✓ Sex: higher incidence in M.

Risk factors:

1- Infections:

- ✓ EBV (Epstein-Barr virus): Burkitt lymphoma
- ✓ Helicobacter pylori: gastric MALT lymphomas "mucosal associated lymphatic tumour" H. Pylori يتسبب في الإصابة بالسرطان

2- Immunodeficiency: immunosuppressive drugs, post transplantation,

3- C.T disorders: e.g. Sjorgen's syndrome. "T lymphocyte infiltrate lacrimal & salivary gland"

4- Chromosomal: Translocation between the long arms of chromosomes 8 & 14

Clinical picture: As Hodgkin's disease but:

1. The disease is more aggressive than Hodgkin's disease
more large and
2. Hard Lymphadenopathy
3. Involved LNs retro-peritoneum, mesentery, and pelvis
4. Abdominal pain & abdominal mass in Burkitt lymphoma
5. Usually disseminated at the time of diagnosis.

Burkitt lymphoma: *on skin*

- M: F — 2 :1
- Presents with bulky central nodal disease + extra-nodal involvement (typically in the abdomen), bone marrow and/or CNS involvement

Investigations: as Hodgkin's disease but no Reed-Strenberg cells

Treatment:

1. Low grade NHL:

- If symptomless and low grade, no ttt may be needed
- Radiotherapy to involved nodal regions
- Single agent chemotherapy e.g. chlorambucil

2. Intermediate & high grade NHL :

- **Combination** chemotherapy : e.g COPP (Cyclophosphamide, Oncovin, Procarbazine, Prednisolone)

3. Lymphoblastic NHL : treated as ALL (acute lymphoblastic leukemia).

Classification of NHL

بدرجہ الی

Indolent lymphomas (Low grade NHL)

- ✓ Follicular lymphoma (grade I & II) 20%
- ✓ **Malt** lymphoma
- ✓ **Small** lymphocytic lymphoma

Aggressive lymphomas (intermediate grade NHL)

- ✓ Diffuse large **B-cell** lymphoma 30%
- ✓ Follicular lymphoma (grade III)
- ✓ Mature **T-cell** lymphomas
- ✓ **Mantle** cell lymphoma

Very aggressive lymphomas (high grade NHL)

- ✓ Burkitt lymphoma 2% Precursor - T lymphoblastic

Multiple myeloma (myelomatosis)

Definition:

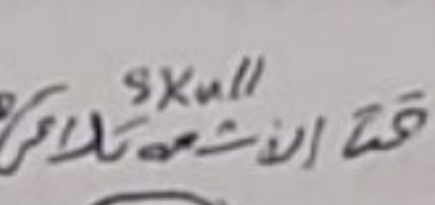
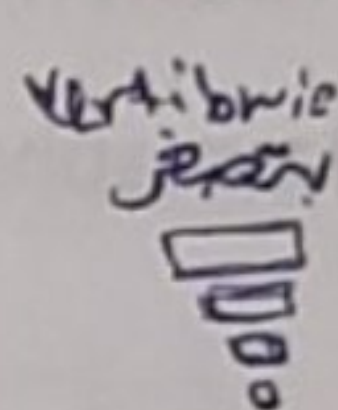
It is a clonal B-cell malignancy characterized by proliferation of plasma cells that accumulate in BM and usually secrete paraprotein, (mainly IgG or IgA and rarely IgD).

Tumour release → osteoclastic activating factor

Clinical picture:

- Multiple myeloma is a disease of elderly and appears usually around the age of 60 yrs
- more common in Males
- The clinical manifestations are due to 4 main items :

1) Bone destruction:

- Most present with bony pain: usually in the back (-75%)
- Pathological fracture 
- Spinal cord compression 
- Hypercalcemia: polyuria, nausea, depression, conjunctivitis

* Alkaline phosphatase normal
BCC It secrete from osteoblast
& this dis affect on osteoclast

2) Replacement of the bone marrow: (BM failure)

- Anemia
- Recurrent infection
- Bleeding

= Gouty nephropathy
urate nephropathy

3) Renal Impairment: Chronic renal failure due to hypercalcemia, hyperuricemia & amyloid deposition "Amyloidosis"

"Nephrocalcinosis"

4) Hyper viscosity (slow circulation):

Due to high paraproteins level IgA or IgG which results in Fatigue, Headache & Blurring of vision

↑ IgM → Waldenström's "hyperviscosity"

Investigations:

1. CBC : Normochromic normocytic anemia, may show rouleaux
2. ESR : always high
3. Serum protein electrophoresis : finding of paraproteins
4. B.M examination : Plasma cell infiltration

Total Plasma Ptw
is: 6-8 "normal"
but percentage
of globulin is high

Bence Jones Ptw in urine could
be high Ig, which excreted
in urine

MCQ 5. **Urine examination** : may be +ve for Bence Jones protein *fragmented Ig excreted in urine*

6. **X-ray bone** : pathological fracture or lytic lesions

7. **Biochemical** : urea, creatinine, Ca with normal alkaline phosphates

*d.t. osteoclastic activity
not osteoblastic activity*

- Suspect **MM** in a patient > 50 with bone pain, anemia, recurrent infection, renal impairment, hypercalcemia, neuropathy & elevated ESR

Treatment:

➤ **Supportive therapy:**

- **Bone disease** : local radiotherapy for localized pain, bisphosphonate
- **Allopurinol** : to prevent urate nephropathy *antagonize OAFs*
- **Antibiotics** : for infections
- **Anemia** : blood transfusion, erythropoietin
- **Hyperviscosity** : plasmapheresis

➤ **Specific treatment:**

- Melphalan and prednisolone
- **Combination** chemotherapy : VAD regimen (Vincristine, Adriamycin and Dexamethasone)

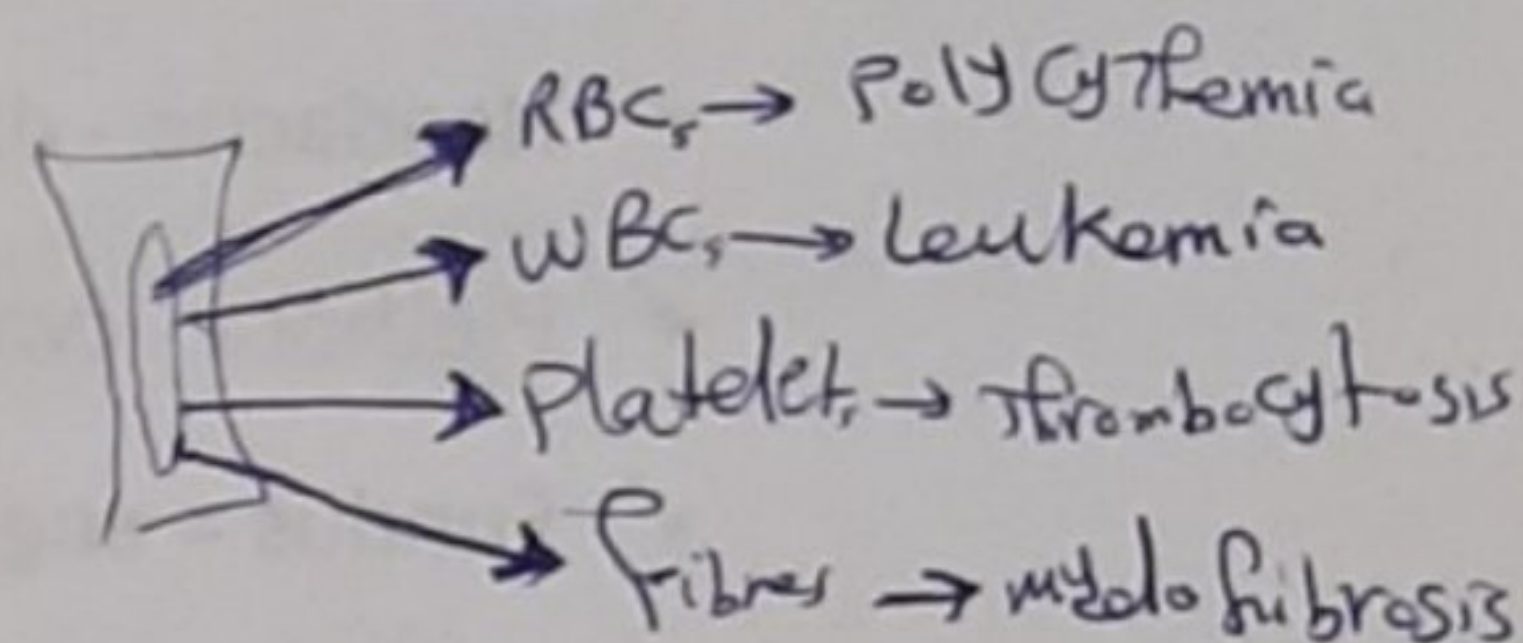
polycythemia

متوقع وبسرعة

DEFINITION : increased RBCs mass that can be detected by :

- Increase number of RBCs OR
- Increase mass of RBCs ($> 6 \times 10^6$) OR
- Increase Hb content ($> 18 \text{ gm } \%$)

Myelo Proliferative disorder



TYPES OF POLYCYTHEMIA

A) Polycythemia rubra vera "1ry polycythemia".

- Unknown benign neoplastic disorder *Preleukemia → converted to CM*
- Stem cell disorder with uncontrolled production of all blood elements including RBCs, WBCs & platelets.
- Characterized by increased sensitivity to all growth & maturation factors
- low level of Erythropoietin *with presence of Jack II gene mutation in more*
- Occure in old age *erythropoietin level → ↓ up to zero* *than 95% of cases of 1ry Polycythemia*

B) 2ry polycythemia "Erythrocytosis".

- Occure in any age
- Increased number of RBCs only
- Due to Increased Erythropoietin.

CAUSES OF 2RY POLYCYTHEMIA

Relative Polycythemia → dehydration
D) Physiological → high altitude

i. Chronic hypoxia (Causes of central cyanosis) :

- ✓ Lung : - Asphyxia - High altitude
- Interstitial lung ds. - Respiratory failure (COPD)
- ✓ CVS : - Congenital cyanotic HDs "fallot's".
- ✓ HB : - MetHb *chemical hypoxia* - Sulpha Hb

ii. Cancer : - Hypernephroma *Tumour in cells which secrete Erythropoietin in D*

- paraneoplastic syndrome

iii. Cushing syndrome

iv. Cortisone therapy

v. Androgens

→ Central cyanosis :- ↑ reduced Hemoglobin > 5 gm%

لا يجمع الـ anemia والـ Polycythemia
"Central cyanosis & Pallor" في نفس المريض

Clinical picture

A) features of Erythrocytosis (hyper-viscosity & hyper-volemia)

Head & Neck

- ✓ Headache - dizziness - vertigo
- ✓ ^{Warm weather} Plethora - cyanosis in exposure To cold "Central"
- ✓ Fundus = engorged retina

UL - LL

- ✓ Warm ± peripheral cyanosis
- ✓ Raynaud's phenomenon

Systemic

- ✓ **CVS** : dyspnea - hypertension ± HF
- ✓ **Lung** : features of P. hypertension

B) Features of thrombocytosis

- Thrombosis
- Paradoxical bleeding (reduction of platelet function)

C) Features of leucocytosis

- Increase of uric acid:- Gout - Renal stones
- Increase of Histamine:- Pruritus - Peptic ulcer "Histamine stimulates H₂ Receptor in stomach"

D) Huge spleen (in cases of 1ry Polycythaemia)

Investigations

- CBC: Pancytosis (Increase all blood elements)
- BM : Hyper-cellularity of all element , Full Blood = Full Bone marrow .
- ESR : Less than expected Zero
- Biochemical : - Uric acid ↑
- Histamine ↑ ^{arise from} "Basophil" → Pruritus & peptic ulcer
- Leukocyte alkaline phosphatase ↑
- The most diagnostic for 1ry form is low level of Erythropoietin

➤ Jack II Gene : +ve in 1ry Polycythemia
erythropoietin → zero in 1ry

Treatment

1) Repeated blood donation

- Aim:- To maintain HB less than 19gm%
- Technique:-
 - Firstly by donation of 500 cc every 5 days accompanied with plasma expander as high molecular weight dextran.
 - Then rate of donation must be adjusted according to the PCV - Hb%

2) Supportive & symptomatic

- ✓ Allopurinol for reduction of uric acid.
- ✓ Anti histaminic
- ✓ Anti-H2 for treatment of peptic ulcer
- ✓ Low dose Aspirin to prevent thrombosis

Allopurinol
Allopurinol

3) Specific therapy (To reduce BM cellularity)

- Radio-active phosphorus
- Chemotherapy : Busulphan or Hydroxyurea

NB : Radio-active phosphorus and Busulphan usually associated with acute leukaemia.

Further types of polycythemia

1st
2nd
Relative
Stress
Physiological

1) Relative Polycythemia

- The mass of RBCs didn't change but concentrated.
- Causes: Dehydration (excessive diuresis - severe diarrhea)

2) Stress Polycythemia

- it is called Benign-Gaisbock's syndrome.
- in middle aged person usually smoker obese with stressful life.

3) Physiological Polycythemia

- Secondary polycythemia in which the production of erythropoietin increases appropriately as a normal adaptation to living at high altitudes.

Myelodysplastic syndrome

PATHOPHYSIOLOGY : Previously called the pre-leukemia

- Acquired stem cell disorders resulting in abnormal random (dysplastic) haematopoiesis manifested by irreversible quantitative and qualitative defects in blood production.
- One-third of the patients progresses to AML.

CLINICAL PICTURE AND TYPES

- Age:- 60 - 75 years (rare in children).
- Sex :- Males are slightly more commonly affected

French-American-British (FAB) classification : 5 categories

- a. Refractory anaemia (RA)
- b. Refractory anemia with ringed sideroblasts
- c. Refractory anemia with excess blasts
- d. Refractory anemia with excess blasts in transformation
- e. Chronic myelo-monocytic leukemia

RA
RA 5-12%
RA 1-5%
RA 1-5%
RA 1-5%

INVESTIGATIONS:

- Bone Marrow : hypercellular with dysplasia and excessive myeloblast (diagnostic)
- Blood film : pancytopenia, macrocytosis and excessive myeloblast

THERAPY

- Bone marrow transplant
- Supportive : blood product support and hematopoietic growth factors (e.g. erythropoietin).

Myelofibrosis

DEFINITION :-

Pancytopenia with huge Hepatosplenomegaly is 70% is

Growth and proliferation of an abnormal bone marrow stem cells resulting in fibrosis that may occur as a reactive following other myeloproliferative disorders, such as polycythemia rubra vera or essential thrombocytosis.

CLINICAL PICTURE :

- Progressive anemia
- Extramedullary haematopoiesis (diagnostic):- HSM
- Recurrent infection and/or bleeding
- The mean survival is 5 years
- Causes of death : infection, bleeding, organ failure, portal HTN and leukemic.

DIAGNOSIS BASED UPON :

1. Normocytic anaemia
2. Blood film : poikilocytosis or tear drop RBCs
3. LDH & neutrophil alkaline phosphatase : raised
4. Bone marrow biopsy:- increased cellularity and fibrosis but late dry
5. Gene mutation (in 50%)

TREATMENT

- a. Supportive : folic acid - allopurinol - blood transfusions.
- b. Specific : Dexamethasone
- c. Alpha-interferon and hydroxycarbamide may play a role.

* Causes of:-
 = lymph node = general lymphadenopathy → No Portal HTN, cirrhosis
 = Splenomegaly
 = Hypersplenism

Dr/M Allam

Hypersplenism

normocytic normochromic

Definition : Reduction of one or more of the blood elements due to hyperfunction of spleen phagocytic activity

Causes of Hypersplenism:

- Primary (Idiopathic) : Cause not found. May be pre-neoplastic (pre-lymphoma).
- Secondary : (all causes of splenomegaly: see below)

Causes of splenomegaly

1) Infection:

• Viral:

- Infectious mononucleosis (IMN)
- Infective hepatitis
- Others: AIDS - 1ry atypical pneumonia

• Parasitic:

- Bilharziasis - Malaria
- Kala-azar (visceral Leishmaniasis)
- Toxoplasmosis - Amoebic abscess

• Bacterial & others:

- Septicaemia & bacteraemia - SBE
- Syphilis (2nry) - Typhoid & typhus
- Brucellosis - TB (military)

2) Congestive splenomegaly:

- All causes of portal hypertension (esp. liver cirrhosis)

3) Haematological:

a. Anaemia

- Iron deficiency anaemia "10%"

- Plummer Vinson \$ (a type of IDA)

- Megaloblastic anaemia (Pernicious anaemia)

- Haemolytic anaemia (except sickle cell anaemia)

b. Haematological malignancies:

- Myeloproliferative: leukaemia or polycythaemia
- Lymphomas: Hodgkin & non Hodgkin's
- Gammopathies: Waldenstrom macroglobulinemia

4) Neoplastic -

- Secondary malignancies
- Primary splenic tumours & cysts

5) Infiltrative:

- Lipoid storage disease: Gaucher's & Niemann Pic ^{نخال}
- Glycogen storage disease: galactosemia
- Amyloidosis

6) Immune collagen diseases:-

- SLE - PAN
- Rh. Arthritis: Still's & Felly's syndrome
- Sarcoidosis

G- Endocrine:

- Acromegaly
- Grave's disease (1ry Thyrotoxicosis).

The causes of massive splenomegaly (>1000 g):

- Chronic Malaria
- Chronic Myeloid leukemia & CLL
- Hairy cell leukemia
- Lymphomas
- Myelofibrosis
- Polycythaemia vera
- Autoimmune hemolytic anemia
- Thalassaemia
- Bilharziasis
- Kala-Azar " Visceral leishmaniasis "
- Gaucher's disease
- Sarcoidosis

Clinical picture of hypersplenism :

Feature of one or more of the following :

- Pancytopenia*
- Features of **anaemia**
 - Features of **leukopenia** (recurrent infection)
 - Features of **thrombocytopenia** (purpura)
 - Feature of **splenomegaly** :
 - Abdominal pain or early satiety $\Rightarrow$ *spleen one of Bed of Stomach*
 - Palpable left upper quadrant abdominal mass or splenic rub. *Bed 12 structures*
 - Percussion:- Castell's sign or Traube's space dullness
 - Features of the **cause**

Four cardinal signs of hypersplenism:-

1. Splenomegaly
2. Cytopenia(s)
3. Normal or hyperplastic bone marrow
4. Response to splenectomy.

Investigations

CBC :- may shows Pancytopenia

- **RBCs:** Normochromic normocytic anaemia + reticulocytosis
- **WBCs:** Leukopenia + lymphocytosis or normal lymphocytic count
- **Platelets:** Thrombocytopenia
- **Reticulocytosis**

BM aspiration : hyperplasia (hypercellularity)

Investigation for the cause

Cr-51 labeled RBCs & platelets: The most diagnostic

Treatment

1. Treatment of the cause
2. Symptomatic treatment :
 - **Anaemia** : Packed RBCs transfusion
 - **Infection** : Antibiotics
 - **Purpura** : Platelets transfusion
3. Splenectomy : The only curable treatment.

Post splenectomy hematological features :

- Thrombocytosis : In about 30% of cases.
- WBC count : Usually normal + mild lymphocytosis and monocytosis.
- RBCs : Abnormalities in RBCs morphology are the most prominent changes and include :
 - **Howell-Jolly bodies**
 - Pappenheimer bodies (contain sideroblastic granules)
 - Target cells
 - Irregular contracted.

Precautions before splenectomy (2-3 weeks before)

- Antibiotics : Long-term penicillin V 500 mg 12-hourly (if sensitive, use erythromycin).
- Vaccination :
 - pneumococcal polysaccharide vaccine repeated every 5 years
 - Meningococcal group C conjugate vaccine
 - Annual influenza vaccine - seasonal -
 - Hemophilus influenzae type b vaccine
 - Meningococcal polysaccharide vaccine : for travellers to Africa/Saudi Arabia, e.g. during Hajj and Umrah pilgrimages.

المرضى الذين يعانون من فقر الدم المزمن ← Chronic anemia
المرضى الذين يعانون من فقر الدم الحاد ← Acute anemia
72
long acting Penicillins
Vaccination as early as possible.

Cr 51 labeled RBCs & Platelets

فول باطن و كبد

Hyposplenism

Refers to the reduction of normal splenic functions, while asplenia refers to the complete absence of splenic functions.

Causes

a) Congenital:-

- May be due to genetic disorders or exposure to environmental factors during gestation.

b) Acquired:

1. splenectomy as in :

- after splenic rupture from trauma or because of tumor.
- as a treatment for diseases e.g. ITP, thalassemia & spherocytosis.

2. Destruction of the spleen (autosplenectomy) e.g. sickle-cell disease.

Clinical picture:

Increase the risk of septicaemia from encapsulated bacteria (Pneumococcus, Haemophilus influenzae and meningococcus).

Management

Antibiotic prophylaxis and Vaccinations (as above)

FUNCTIONS OF LYMPH NODES

- 1- Filtration and removal of bacteria & foreign bodies from lymph stream
- 2- production of lymphocytes
- 3- extra-medullary haematopoiesis

Generalized lymphadenopathy

1. Infective

- **viral** : IMN - infective hepatitis - AIDS - measles - rubella
- **protozoa** : toxoplasmosis
- **bacterial** : septicaemia - syphilis (2ry) - TB - brucellosis

Infection
Haematological malignancy
neoplastic
infiltrative
miscellaneous

2. Haematological malignancy : Leukaemia , Lymphoma , multiple myeloma

3. Neoplastic : Metastasis or severe 1ry tumours.

4. Infiltrative : - lipoid storage disease (Gaucher's) - Amyloidosis

5. Miscellaneous :

- **Collagen** : SLE , Rh. arthritis (esp. Felty's & still's disease)
- **Sarcoidosis**
- **Serum sickness**
- **Hyperthyroidism** (Grave's disease)
- **Drug reaction** : DPH , PAS , INH , streptomycin

DIAGNOSIS OF GENERALIZED LYMPHADENOPATHY

a- History & complaint:

- **Age** : Middle age in TB - old in CLL
- **Onset & course** : acute in infection - Acute leukaemia - gradual in CLL
- **Rash** : SLE - measles
- **Fever** : pel ebstein in Hodgkin .
- **Bleeding & bony pain** : Leukemia
- **TB reaction (toxemia)**: in TB

b- Past history : of TB therapy or Syphilis

c- Examination:

- 1- Bleeding gums , sternal tenderness , purpura : leukaemia
- 2- Huge spleen : CML - lymphomas
- 3- Joint affection : collagen diseases

4- Glands :-

- a- German measles & IMN: usually soft and firm occipital or cervical
- b- TB: matted
- c- Hodgkin: smooth, painless, rubbery and discrete
- d- Lymphosarcoma: hard and fixed
- e- Syphilis & lymphoma: enlarged epitrochlear glands

INVESTIGATIONS:

- 1- Blood picture and BM: for leukaemia, lymphoma.
- 2- LN biopsy: the most diagnostic.
- 3- Specific tests: e.g. VDRL for Syphilis - ANA for SLE - Paul Bunnell test for IMN.

Von williprent factor - VWF..
 Franchin Base of Platelet aggregation
 Adhesion carry factor VIII
 Dr/M. Allam

Hemostasis

Control of bleeding after injury and insurance of adequate blood flow.

Haemostasis is composed of 4 major events:

1. Initial Phase of vascular constriction: To limit the flow of blood to the area of injury
2. Platelets aggregate: To the site of injury, forming a temporary platelet plug.

(platelets release ADP and TXA₂ which activate additional platelets)

N.B. Platelets secrete serotonin, phospholipids, lipoproteins, and other proteins important for the coagulation cascade.

3. Clot formation "Coagulation system": Fibrin mesh forms and entraps the plug.

N.B. IF the plug contains only platelets it is termed a -white thrombus. if red blood cells are present it is called a red thrombus.

4. Finally repair: of blood vessels and activation of fibrinolytic system.

Coagulation System occurs through Three pathways:

lead to the formation of a fibrin clot

❖ The Intrinsic Pathway:

Activated by Exposure of vascular wall collagen or roughness of endothelium, leading to activation of Factor XII

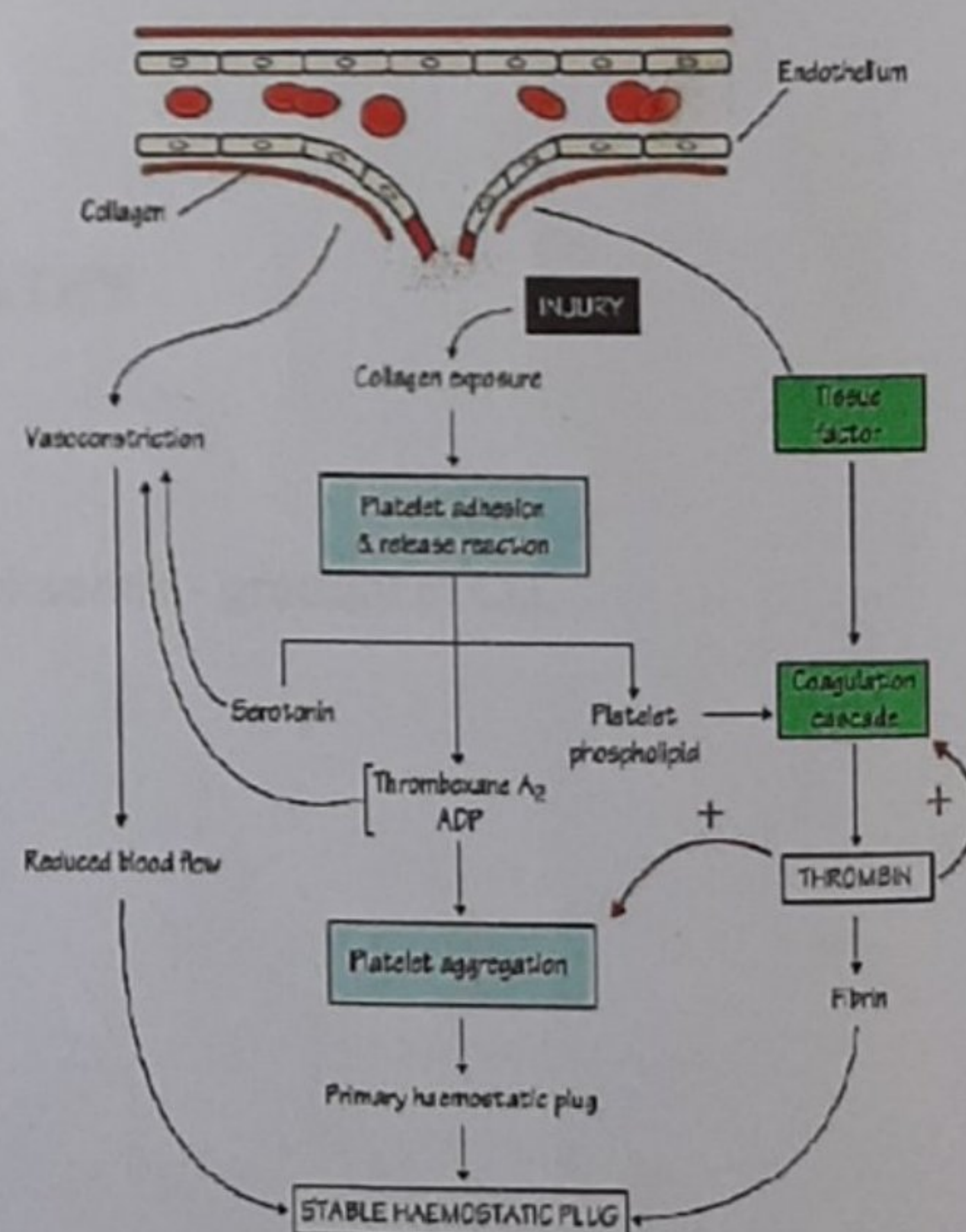
❖ The Extrinsic Pathway:

injury or trauma → release of tissue factor "FIII" which binds to Factor VII creating a complex. This complex activates Factor X to Xa.

❖ The Combined Pathway:

Activated Factor X converts inactive molecule prothrombin to the active thrombin.

(in the presence of Factor Va), Thrombin then cleaves fibrinogen into fibrin, Which then polymerizes to form fibrin strands.



Coagulation Factors

black : both pathways

Green : intrinsic

Blue : Extrinsic

I	- Fibrinogen	Both
II	- Prothrombin	Both
III	- Tissue Factor (tissue thromboplastin) (PT test)	Extrinsic
IV	- Calcium	Both
V	- Proaccelerin, labile factor, accelerator (Ac-) globulin.	Both
VII	- Proconvertin , Stable F	Extrinsic
VIII	- Anti-hemophiliac factor.	Intrinsic
IX	- Christmas Factor (anti-hemophilic B)	Intrinsic
X	- Steuart-Prower Factor	Both
XI	- Plasma thromboplastin antecedent (PTA)	Intrinsic
XII	- Hageman Factor	Intrinsic
XIII	- Fibrin stabilizing factor (FSF)	Both

Steps of coagulation pathways (Coagulation Cascade).

Extrinsic pathway :

- Depends on Factors III & VII
- Assessed by : prothrombin time "PT"
- Normal PT = 10 : 14 sec .

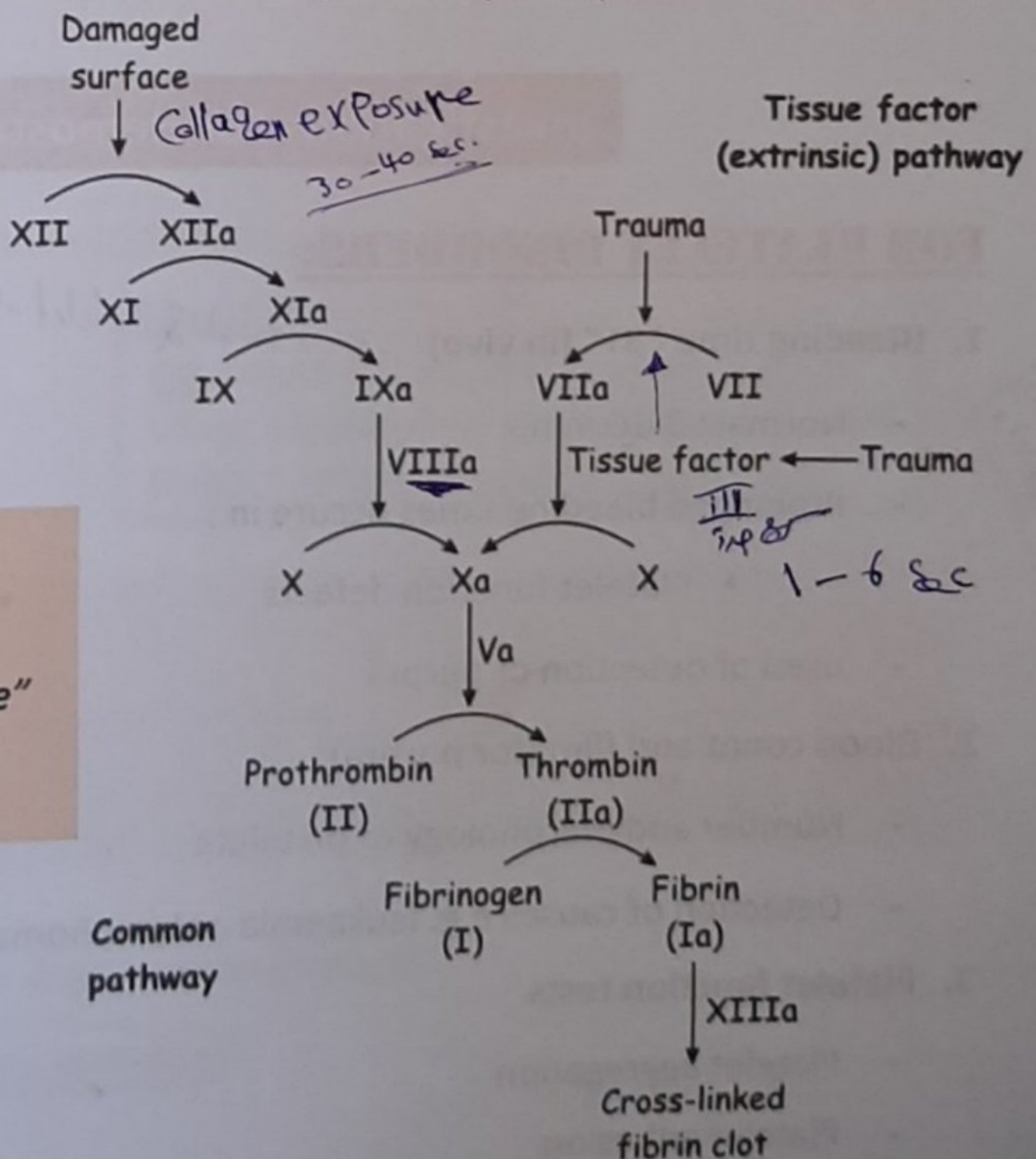
Intrinsic pathway :

- Depends on Factors " XII , XI , IX & VIII "
- Assessed by : "APTT"
"Activated Partial Thromboplastin Time"
- normal "APTT" = 30 : 40 sec.

Common pathway :

- Begins by Activation of factor X
- $X \rightarrow II \rightarrow I \rightarrow XIII$

Contact activation (intrinsic) pathway



NB. 12den's factor → resistance to Factor V and Protein C → thrombosis

Hematology

And it's the commonest inherited thrombophilia

Dr/M. Allam

Regulators of hemostasis

1- Protein C & S: ^{inactivation factor V} Major physiological anti-coagulant. It is a vitamin K-dependent.

2- Anti-thrombin III

Degrades thrombin, Factors IX, X, XI and XII.

Quantitative or qualitative deficiency of anti-thrombin (inborn or acquired, e.g. in proteinuria) leads to thrombophilia.

3- Tissue factor pathway inhibitor (TFPI): Limits the action of tissue factor (TF). ^{Anti thrombin III} ^{loss in nephrotic syndu} so heparin not effective in this cases bec. it activate Anti thrombin III and this factor is lost. give LMWH → act on factor X

4- Plasmin (fibrinolytic system): Tissue plasminogen activator (t-PA) split plasminogen to plasmin (t-PA synthesized and secreted by endothelium)

5- Prostacyclin (PGI): Released by endothelium and inhibits platelet activation.

NB. Hemostatic disorders are classified into:

Purpra → defect in Blood vessels or defect in platelets

Coagulopathy → defect in coagulation system

Investigations For Hemostatic Disorders

FOR PLATELET DISORDERS:

1. Bleeding time "BT" (in vivo) ^{.. Blood vessels & Platelet aggregation.}

- Normal : 3-10 min.
- Prolonged bleeding times occur in :
 - ♦ Platelet function defects
 - ♦ Platelet counts $< 80 \times 10^9/L$.
- used of detection of purpra

2. Blood count and film (for purpra)

- Number and morphology of platelets
- Detection of causes e.g. leukaemia or lymphoma.

3. Platelet function tests

- Platelet aggregation
- Platelet adhesion
- Clot retraction

الوقت الذي يخرج الدم من الجرح
والوقت الذي يوقف الدم
والوقت الذي يجمع الدم

Natural anticoagulant - PTV C
 arise from  - PTV S
 - Antithrombin III

FOR COAGULOPATHY:

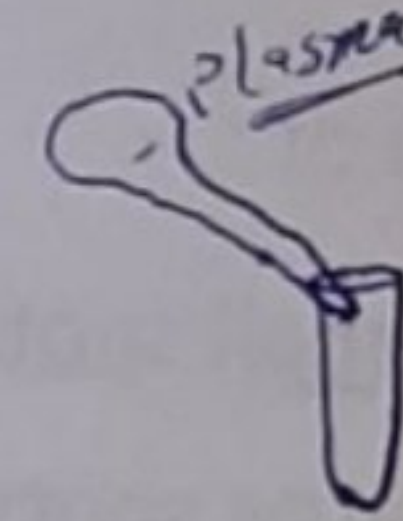
- 4- Bleeding time & platelets : Normal
- 5- Clotting time : prolonged (in vitro - Normal:- 5-10 m) .

PLUS

> Intrinsic pathway:

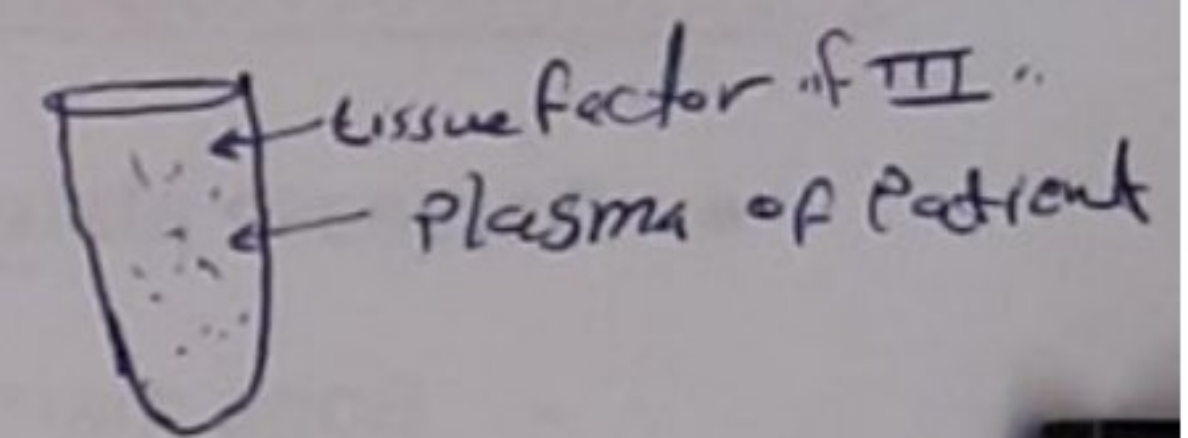
Coagulation Factor ~~intrinsic~~ ^{intrinsic}

- ✓ By Activated partial thromboplastin time (ApTT)
- ✓ Technique : Surface activator + plasma
- ✓ Normal 30 -40 sec.
- ✓ Prolonged in : DIC , Heparin & factors (1,2,5,8,9,10,11,12) deficiency



> Extrinsic pathway:

- ✓ By Prothrombin time (PT)
- ✓ Technique : Tissue thromboplastin (factor III) + ca + plasma
- ✓ Normal 10 -14 sec.
- ✓ Prolonged in :
 - Deficiency of factor : 1,2,5,7,9,10 (1975)
 - DIC, LCF & Oral anticoagulant



> Fibrinolytic system

- Plasma fibrinogen
- Fibrin Degradation Products.
- Others : (Euglobulin clot lysis time (ELT) - plasminogen - TPA -PAI-1).

- Assessment of fibrin by

- 1- Fibrin level
- 2- FDPs
- 3- Thrombin time (clotting time) :

- Technique: Thrombin + pt. plasma
- Normal : 12-20 sec.
- Value: Tests the conversion of fibrinogen into fibrin
- prolonged in: - Heparin - DIC
- - Hypofibrinogenaemia - Fibrin degradation product

International normalization ratio - Warfarin ^{anticoagulant}

★ INR = $P_t.PT / \text{control PT} = \text{Normal } 0.8-1.2$
 Value: Adjusting oral anticoagulant at 2-3 INR
 Except : Prosthetic valve at 2.5 - 3.5 INR

D-dimer : - Measures fibrinogen/fibrin degeneration products

- Raised in: DVT & Pulmonary embolism

Factor Assay :

Used to confirm coagulation defects , especially where a single inherited disorder is suspected.

Purpura

Latin, purpura, meaning "purple"

Definition : Appearance of spontaneous bleeding causing red or purple discolorations of skin, in the form of :

- ✓ Small spots are called Petechiae (Not blanch by pressure) less than 1cm
- ✓ large spots are called Ecchymosis greater than 1cm.

Aetiology :

A) Platelet defect Purpura (Intravascular P.)

1- Thrombocytopenic purpura (defect in platelet number) :

- Decrease platelet production
 - Bone marrow failure : as Aplastic anemia
 - Megaloblastic anaemia (B12 or folic)
 - Bone marrow replacement as : leukemia & malignancy
 - Drugs: cytostatic drugs & thiazides
- Increase platelet destruction
 - Idiopathic / immune : ITP , SLE , Evan's \$
** Idiopathic / immune*
** Allo antibodies*
never splenectomy
 - Allo-antibodies: post blood transfusion.
 - Mech : prosthetic valves , haemodialysis
 - Hypersplenism
 - Massive Blood transfusion → dilutional thrombocytopenia.
- Increased platelet consumption : DIC & TTP "thrombotic thrombocytopenic purpura"

2- Thrombocyto-pathies (thromboasthenic purpura) defect in function

- Congenital
 - Glanzman's disease: defective platelet aggregation
 - Bernard - Soulier disease: giant platelets + defective platelet adhesion
 - Von - Willebrand disease *defect in platelet aggregation*
- Acquired
 - Drugs : aspirin (thromboxan A2 inhibitor) , Heparin , Antibiotics ,
 - Uraemia : ARE , CRF
 - Myeloproliferative : polycythaemia
 - Essential thrombocytosis: excess platelet interferes with Thromboplastin.

Toxins of liver cell failure & kidney failure

B) Vascular purpura

1- Hereditary

Capillary & Arteries لا يندمج

- Hereditary Telangiectasia : Weber - Osler S.
- CT disorders : Marfan's syndrome , Ehler-Danlos Syndrome . weakness of capillary wall.
- Vascular Hemophilia (Von Willebrand's D.)

Purpura

2- Acquired

4 ITC 35 2M

- Infective : SBE - P. fulminans
- Immunological : Henoch schoneilin purpra.
- Iatrogenic : steroids , sulpha , chemotherapy
- Idiopathic : purpura simplex (Devil's pinch) ☹️😊 self limited
- Collagen ds : SLE , Vasculitis syndromes....
- Senile purpura
- Scurvy : vit C deficiency.
- Self induced " Factitious " عصبية
- Malignancy
- Menopause .
- Cushing syndrome

١٢٣٤٥٦

Clinical picture:

1-Feature of cause

2- Bleeding:

a- In skin:

- Spontaneous petichae
- Rare ecchymosis as size of pin head.
- They occur in groups on limbs & trunk.
- Recent spots are red in colour, later change into brown then disappear.

b- In mucus membrane:

- Epistaxis, bleeding gums, haematuria, haemoptysis

c- In internal organs: Especially cerebral hemorrhage (cause of death)

Hess Test

- **Definition :** *In vivo assessment of collagen matrix, vascular endothelium and platelet adhesion and aggregation*
- **Technique :** *A sphygmomanometer is inflated to between the systolic and the diastolic pressures for 5 minutes*
- **Positive test if :** *more than 5 petichae would occur in a 5cm diameter circle.*

Bleeding time

- **Technique :**
 - *a sphygmomanometer on the upper arm is inflated to 40mmHg.*
 - *a skin incision 5mm long and 1mm deep is made on the extensor surface of the forearm.*
 - *Filter paper is used to blot the edges of the wound at 30 second intervals until the bleeding stops.*
- **Normal is 3 - 9 minutes**
- **Prolonged Bleeding time is due to :** *Platelet deficiency or abnormality & Von Willebrand factor abnormality or deficiency*



Rumple-Leede phenomenon, most pronounced in patients with a thrombocytic or vascular bleeding diathesis. When a blood pressure cuff is applied and inflated to a pressure that is between the arterial blood pressure and diastolic pressure, petechial skin hemorrhages appear on the arm within five minutes.

Idiopathic Thrombocytopenic Purpura (ITP)

The commonest type of thrombocytopenic purpura

Aetiology:

- Auto-immune:** - due to presence of antibody IgG for platelet (ITP factor)
- the spleen removes platelets modified by antibody.
- The released antibody:** prevents megakaryocytes from producing platelets
- Capillary defect:** probably ITP factor causes increase in-capillary Permeability

Clinical picture: clinical forms

1- **Acute ITP** mostly viral infection → forms antibodies → attack Platelet

- ✓ **Age:** Children 2-9 Y.
- ✓ **C/P:** - Acute onset of haemorrhage from Mucous Membranes, Purpura, Orifices, Internal bleeding (cerebral haemorrhage)

- Spontaneous remission in 10 to 30 days
- mostly due to viral infection.

2- **Chronic ITP** صائلي

- ✓ **Age:** Females 20-40 Y.
- ✓ **C/P:** - Chronic intermittent course with remission & exacerbation
- Spleen is commonly palpable

Female + Rubric eruption + Heavy Period

Investigation:

- ↓ platelets number
- Prolonged bleeding time
- Positive Hess test.
- Coagulation tests are normal
- BM:** abundant megakaryocytes but show no evidence of excessive budding.
- Platelet autoantibody:** +ve in 70% of cases

To exclude malignancy

Diagnosis:

for diagnosis of idiopathic variety, exclude other causes and types:

- Absence of fever or constitutional symptoms
- Absence of Lymphadenopathy or marked splenomegaly (10% have just palpable spleen)
- Normal ESR & serology evidence of Autoimmune dis

CLINICAL EFFECTS CAUSED BY DIFFERENT LEVELS OF PLATELETS COUNT	
10^3	- Clinical defect
> 500	- Haemorrhage or thrombosis
$500 - 100$	- Paradoxical Bleeding - No clinical effect
$100 - 50$	- Moderate haemorrhage after injury
$50 - 20$	- Purpura may occur - Haemorrhage after injury
< 20	- Purpura common - Spontaneous bleeding from mucous - Intracranial haemorrhage (rare)

High Risk Group

Treatment:

1- Conservative:

- In children (self limited) or adult with mild form.
- Restrict physical activity
- avoid unnecessary operations & aspirin intake

2- Drugs:

a- Prednisone :

- ✓ children 1 mg/kg/day - adult 40-50 mg/day for 2-4 weeks.
- ✓ After platelet count retunes to normal, taper gradually over 2-4 weeks.

b- Immunosuppressives :

- ✓ Cyclophosphamide or Azathioprine in resistance cases

c- Immunoglobulins : المناس الحلو

- ✓ High IV doeses of to block Fc receptors in spleen (transient).

d- Danazol : Non virilising androgen in steroid resistant cases.

Androgenic effect

3- Others:

▪ Platelet transfusion:

In severe bleeding or emergency-surgery (rapidly destroyed by autoantibody and expensive)

▪ Plasmapheresis: To remove autoantibody

4-Splenectomy: in steroids failure or relapses & in fulminant cases (adult form).

Henoch-Shoenlein Purpura (HSP)

Vascular

Anaphylactoid / Allergic purpura

Cause:

Allergic form of purpura (type III hypersensitivity), affecting children, usually following streptococcal sore throat by 1-3 week (like Rh fever) *IGA*

Pathogenesis:

Wide spread capillaritis & arteriolitis with deposition of IgA & components of alternate pathway of complement system

Clinical picture:

Characterized by tetrad of

- 1- Purpura : Over extensor surface of arms, legs, buttock
- 2- Arthritis : Tender swelling of joint with Peri-articular Haemorrhage
- 3- Abdominal pain : Due to affection of sub-mucosal intestinal vessels, leading to extravasation of blood in wall of intestine & bloody-stools (simulating intussusception)
- 4- Glomerulonephritis : nephritic syndrome. (5-10% pass to CRF)
immune complex deposit in kidney

Investigation:

- 1- Prolonged bleeding time - positive Hess test.
- 2- Normal Coagulation tests and platelets count.
- 3- IgA + C3:- +ve in 70% of cases
- 4- Tissue biopsy is +ve for IgA

Treatment:

- 1- Corticosteroids
- 2- Symptomatic ttt



Purpura Fulminans

Cause : Acute infection as scarlet fever, and meningococcal septicemia

C/P : wide spread purpura & Acute vasculitis infarction .

Complications :

- Shock
- Acute adrenal necrosis (Addisonian crisis) *Supra renal dysfunction due to closure of blood vessels*
- DIC & wide spread haemorrhages all over the body (Waterhouse-Friedrichsen syndrome)

meningitis
↓
Cytokines
↓
Platelet activating factors
↓
Thrombosis → *Bleeding "DIC"*
"consumption of platelets"

COAGULATION DEFECTS (COAGULOPATHY)

Classification

Hereditary	Acquired
<i>Commonest</i> → 1- Hemophilia (factor 8 deficiency) 2- Christmas disease (factor 9 def.) 3- Para hemophilia (factor 5 def.) 4- Afibrinogenemia <i>Factor I</i> 5- Dysfibrinogenemia	1- Organ failure : liver, renal F. <i>↳ Toxin interfere with action of coagulation factors</i> 2- Vitamin K deficiency 3- DIC 4- Circulating anticoagulants: e.g. SLE 5- Drugs: heparin, oral anticoagulants, fibrinolytics.

General features:

- Prolonged bleeding** : *Should be after Trauma not spontaneous*
 - Since birth : circumcision , ear piercing as in hereditary causes
 - After lacerations , tooth extraction , trauma , IM injection etc.
- Skin & SC tissue** :
 - Ecchymosis** " spont. Or traumatic " *↳ Skin muscle S.C*
 - Soft tissue hematoma**
 - Deep bleeding** : in muscles , retroperitoneal , GIT & Cerebral Hge.
 - External bleeding** : Epistaxis , Haematemesis , Haemoptysis , Haematuria
Haematochezia (bleeding per rectum)
- Joints** : spontaneous *↳ Intra articular Hge* Hemoarthrosis (commonly in knee → Ankle → Hip → Elbow)
- Acute & Chronic post hemorrhagic anemia.**
- Neuropathy** : due to nerve compression by hematoma
- Infections** : from repeated blood transfusion (HCV , HBV , HIV).



FACTOR VIII (ANTI-HEMOPHILIC . F) DEFICIENCY

- Factor VIII is formed of 3 components
- Its synthesis by 2 genetic loci one on X chromosome & on one autosome. *X-linked*
- Its deficiency is the commonest congenital coagulopathy & can result in either one of 2 diseases:
 - Haemophilia A**: X-linked- due to formation of abnormal VIII AHF component.
 - Von-Willebrand syndrome**: autosomal dominant, deficiency of the 3 components.

"Dipin" ~~Tipin~~

Hemophilia A

Aetiology

- X-linked recessive disorder : only males are affected Females act as carrier (rarely affected)
- There is abnormal VIII-AHF component of factor VIII
- Other components are normal or even increased.

The severity of the disease depends on the factor activity

	Factor Activity	Cause Of Hemorrhage
MILD	More than 5 %	Major trauma or surgery
MODERATE	1 – 5 %	Mild to moderate trauma
SEVERE	Less than 1 %	Spontaneous hemoarthrosis

Clinical picture: as general clinical picture (see above)

Investigations:

- 1- Platelet count , function & bleeding time : Normal
- 2- Clotting time : Prolonged (May be Normal in mild cases)
- 3- PT : Normal
- 4- PTT : Prolonged (the defect is in intrinsic pathway)
- 5- Factor VIII AHG Assay is Diminished (Normal= 50-200IU / ml).

Other components are normal or even increased.

- 6- Microcytic hypochromic anaemia may result from prolonged bleeding

Treatment :

A- General:-

- Genetic counseling
- Avoid Aspirin, Trauma, Heavy sport, Operation, IM injection
- Immunization against Tetanus
- AHG as prophylaxis

B- Symptomatic:-

- 1- Minor local wounds : local pressure, topical thrombin.

- ### C- Replacement

- ### D- Others:

- ### Haemophilia B (Christmas disease)

- fresh or stored blood transfusion (factor IX is stable)

C/P : simulates hemophilia

88

VWF
Base of platelet aggregation adhesion
Carry factor VIII
Dr/M. Allam

Vascular Haemophilia

VWD (Von - Willebrand Disease)**Definition:**

- It is inherited in an autosomal dominant disease
- Complex syndrome characterized by deficient formation of all the 3 components of F VIII.
 - Deficiency of factor VIII VWF: Results in prolonged bleeding time due to defective platelet adhesiveness
 - Deficiency of factor VIII AHF: Results in Haemophilia
 - Deficiency of factor VIII-Agn

Clinical picture: mixture of purpura & haemophilia.

Investigations: prolonged both coagulation time & bleeding time.

Treatment: as of hemophilia A (see Later)

	Von-Willebrand Disease	Haemophilia
Transmission	Autosomal dominant	X-linked recessive
Deficiency	3 component of factor 8	Factor 8 AHF
Clinical picture	Purpura + Ecchymoses	Ecchymoses & haemoarthrosis
Investigations (+)	bleeding + coagulation time	coagulation time only

Hypo-prothrombinemia

Causes: vitamin K deficiency (responsible for factor 2, 7, 9, 10 synthesis)

1972

- Low intake : Rare
- Low absorption : Malabsorption, obstructive jaundice (fat soluble vitamin)
- Low utilization : Anticoagulants, liver failure (refractory).
- Sterilization of bowel : prolonged use of Antibiotics.
- Hemorrhagic disease of new born : as a result of hepatic immaturity, inadequate intake, delay gut colonization by bacteria.

Clinically: coagulopathy as usual - haemoarthrosis is rare - feature of cause

Investigation: prolonged coagulation time, PT & PTT

Treatment: Ttt of cause plus Vitamin K1- IM or IV

How to diff bet / Hepatic cell failure
89
A/ Parental diet K
jaundice
obstructive jaundice

Disorders of Fibrinogen

Elevated plasma fibrinogen

- Inherited disorders in fibrinogen
- coronary artery disease
- hypertension
- hypercholesterolemia
- hypertriglyceridemia.
- Pregnancy, menopause and use of oral contraceptives
- Acute-phase response
- Diabetes mellitus
- Peripheral artery disease
- Hyperlipoproteinemia
- Smoking

Afibrinogenemia Complete lack of fibrinogen (Autosomal Recessive)

- C/P :**
- Neonatal umbilical cord hemorrhage
 - Ecchymoses
 - Mucosa hemorrhage , Internal hemorrhage and Recurrent abortion.

Hypofibrinogenemia . (normal = 250-350mg/dL)

Def :- ↓ Fibrinogen levels below 100mg/dL either acquired or inherited

C/P :- As afibrinogenemia but less severe

Dysfibrinogenemia

Def : Heterogeneous affection of fibrinogen function (Presence of dysfunctional fibrinogen).

C/P : Hemorrhage, spontaneous abortion and thromboembolism.

Thrombocytosis/thrombocythaemia

(Increased platelet count)

❖ **Essential or primary thrombocytosis:** *JAK2 Gene mutation & TTT by Hydroxy urea*

This is defined as a non-reactive chronic myeloproliferative disorder that causes chronic elevation of platelet count

❖ **Reactive or secondary thrombocytosis:**

- Acute inflammatory or infective disorders
- Chronic inflammatory dis. e.g. Tuberculosis, Rheumatological disorders
- Spleen : Post-Splenectomy - Splenic hypo-function/hypo-perfusion - Asplenia
- Trauma & Acute Hge
- Iron-deficiency anemia
- Some leukaemias (particularly CLL or CML)

Disseminated Intravascular Coagulopathy

Consumptive coagulopathy (DIC)

Definition :

Disseminated coagulation all over the body (as micro-thrombi) leading to depletion of platelets and coagulation factors, resulting in the massive bleeding.

Pathogenesis :

1. The initial micro-thrombi either formed after activation of :

- Intrinsic (endothelial injury as caused by sepsis) OR
- Extrinsic (intravasation of abnormal material as amniotic) pathway.

2. Then depletion of platelets and coagulation factors:

- Resulting in the massive bleeding.

N.B : Regardless of the triggering event of DIC once initiated the pathophysiology of DIC is similar in all conditions.

Etiology :

1. Obstetric (most common)

- Abortion & Abruption placenta *early separation of placenta*
- Amniotic fluid embolism
- Hemorrhagic shock
- Dead fetus syndrome

4. Tissue trauma :

- Burns & shock
- surgery or Accidents
- heat stroke

2. Infections : *Cytokines*

- Severe bact. Infections , toxemia & septicemia (as meningitis & pneumonia)
- Fungi & viruses
- Rickettsia & malaria
- Viral hemorrhagic fevers

5. Liver diseases :

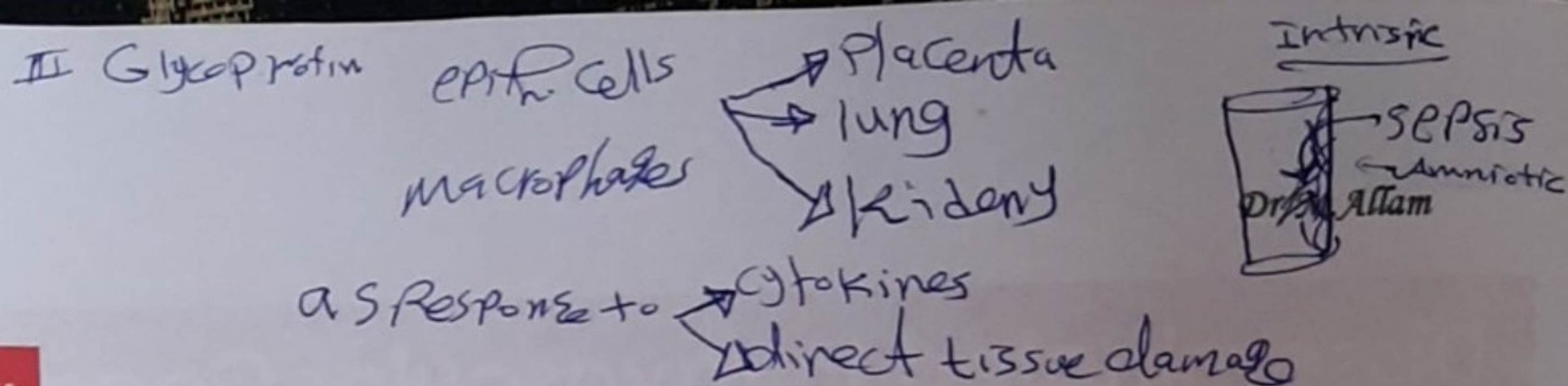
- Acute fulminant hepatic failure.
- Cirrhosis

3. Cancer : *F_{III} due to destruction of cytokines → platelet activation factor.*

- Acute promyelocytic leukemia
- Disseminated adenocarcinoma
- Stomach & pancreatic cancer

6. Others :

- Massive or incompatible BT
- Cerebral infarction or hemorrhage
- Aortic Aneurysm
- Giant hemangioma



Clinical picture:-

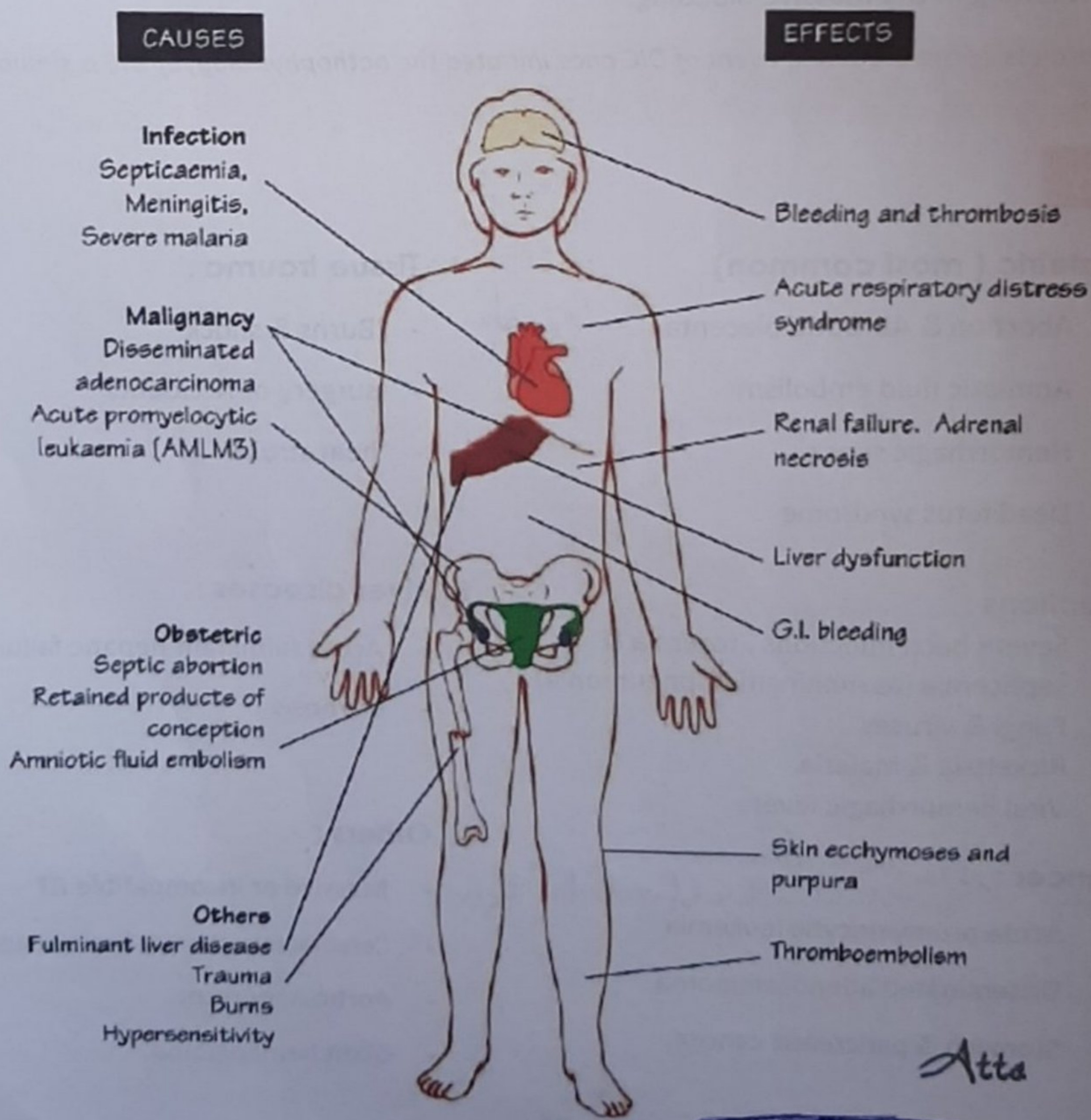
It is a paradoxical situation in which there is a high risk for simultaneous catastrophic thrombosis as well as massive hemorrhage.

Acute DIC

- **Bleeding > thrombosis**
- **Multiple bleeding sites:**
 - Ecchymoses of skin and mucous membranes
 - Visceral hemorrhage
 - Shock and multi-organ failure

Chronic DIC

- **Thrombosis > bleeding**
- **Micro-thrombosis:**
 - Deep venous or arterial thrombosis.
 - Superficial venous thrombosis
 - Multiple and serial thrombotic episodes
 - Chronic organ dysfunction



Investigations

- i. Prolonged All Coagulation times : $\uparrow$ PT , APTT , TT & BT
- ii. $\downarrow$ Platelet count
- iii. $\downarrow$ Fibrinogen levels
- iv. Fibrin degradation products (FDPs)
- v. D-dimer tests (markers of fibrinolysis)

The most specific test is fibrin degradation products (FDPs)

N.B Chronic DIC may be asymptomatic and only mild platelets depletion and FDPs elevation are detected with other parameters Within normal

Treatment

- Treatment of the underlying cause
- **Specific treatment of DIC (highly controversial)**

1) Acute DIC

- Without bleeding or ischemia $\rightarrow$ No treatment
- With bleeding
 - Blood components as needed
 - Fresh frozen plasma:- may result in formation of thrombosis
 - Cryoprecipitate
 - Platelet transfusions:- if counts are less than 5,000-10,000/mm or massive hemorrhage was occurring.
- With Ischemia: Life threatening thrombus (coronary or cerebral) so give Anticoagulants

2) Chronic DIC

A- Without thromboembolism

- No specific therapy needed but prophylactic drugs
- Patients at high risk of thrombosis low-dose heparin, LMW heparin may be used

B- With thromboembolism

- Heparin or LMW-heparin then warfarin
- If warfarin is unsuccessful, long-term use of LMW-heparin
- In some situations, infusion -with antithrombin or Recombinant activated protein C may be necessary.

Thrombophilia

Hyper-coagulable state

Aetiology:

1- Inherited (< 50 years of age)

- Antithrombin deficiency (>50% of inherited thrombophilias)
- Defects in protein S, C, antithrombin
- Other rare disorders

2- Acquired disorders

- Malignancy , Surgery or trauma
- Pregnancy, oral contraceptives, hormone replacement, tamoxifen
- Immobilization, congestive HF, heparin therapy
- Hyperhomocysteinemia
- Hyperviscosity (multiple myeloma, polycythaemia vera)

3- Other (antiphospholipid antibody syndrome, nephrotic syndrome)

Clinical picture:

- Purpura fulminans
- Superficial or deep vein thrombosis, pulmonary embolism
- Thrombosis of "unusual" venous circulations (e.g., cerebral, hepatic, mesenteric and renal veins - possibly arm, portal and ovarian veins – not retinal vein or artery)
- Warfarin-induced skin necrosis .
- Possibly arterial thrombosis (e.g., stroke, acute myocardial infarction)
- Recurrent fetal loss
- Possibly complications of pregnancy (e.g., intrauterine growth restriction, stillbirth, severe pre-eclampsia, abruptio placentae)

Investigations:

directed for assessment of the affected vessels + the coagulation profile (normal)

Treatment:-

- Prophylactic. Anticoagulant PLUS TTT of the affected system (e.g. ttt of PE)

Complications of Blood transfusion

1- Early complications

- i. Haemolytic reactions (Immediate & Delayed)
- ii. Hypothermia
- iii. Hyperkalaemia Fragility of RBC
- iv. Transfusion-related acute lung injury d. to Cytokines which Transmitted with Blood which attack alveoli
- v. Thrombophlebitis
- vi. Circulatory overload
- vii. Citrate toxicity
- viii. Clotting abnormalities (after massive transfusion)
- ix. Non-haemolytic febrile reactions
- x. Allergic reactions to proteins, IgA
- xi. Air embolism
- xii. Reactions secondary to bacterial contamination

2- Late complications

- Infection

- ✓ Viral (hepatitis A, B, C, HIV, CMV)
- ✓ Bacterial (Treponema pallidum, Salmonella)
- ✓ Parasites (malaria, toxoplasma)

الدم المتقول بهام
الدم الطبيعي

Graft-vs-host disease

- Iron overload (after chronic transfusions)
- Immune sensitization (Rhesus D antigen)

Anticoagulants

Indications

- Recent MI
- Embolism → (Cerebral, pulmonary or Cardiac)
- AF
- Prosthetic valve
- Stroke in evolution
- DVT

Contra-Indications

- Bleeding tendency
- Angiomatous malformation
- LCF
- Peptic ulcer
- Open TB
- Aspirin use
- Severe HTN or Dissecting aneurysm

	Heparin	Oral Anticoagulants
Action	- Decrease thromboplastin - Decrease thrombin Anti-platelets	Anti Vit. K (factors; II, VII, IX and X)
P-kinetics	Rapid action for short duration	Late action after 3 days
Dose	5000 IU IV(\4-6h) SC(\8-12)	Loading : 10 mg \3 days Maintainance : 1 – 10 mg/day
Control	Aptt (2-3 normal)	PT – INR
Side effect	- Bleeding Hypersensitivity - Osteoporosis Decrease platelets	- Teratogenic - Drug interaction
Antidote	Protamine sulphate	Vit K IV

LMW - heparin

- **Action** → Anti factor X
- **Pharmacokinetics** → Long (used once)
- **SE** → Less bleeding complications (safe)
- **Control** → No dose adjustment is needed & no monitoring needed.

	ITP	H.S.P	HEMOPHILIA	VWD	DIC
BLEEDING TIME	↑	↑	NORMAL	↑	↑
PLATELET COUNT	↓	NORMAL	NORMAL	NORMAL	↓
PLATELET FUNCTION	NORMAL	NORMAL	NORMAL	↓ ↓ ↓	NORMAL
COAGULATION TIME	NORMAL	NORMAL	↑	↑	↑
PTT	NORMAL	NORMAL	↑	↑	↑
PT	NORMAL	NORMAL	NORMAL	NORMAL	↑
FDP	NORMAL	NORMAL	NORMAL	NORMAL	↑ ↑ ↑
SPECIFIC	ANTIPLATELET AB & IG-G	IG A & C3	FACTOR VIII	VWF	FDP

Maged Muhammed

Coagulation Profile

Ab on Platelets
&
destruction
by spleen

Immune complex
deposition in
bl. vs
↓
Vasculitis

defect in
Factor VIII
"intrinsic"

no P. adhesion
& defect in
Factor VIII

Intrinsic pathway
large platelets
↓
Platelets consumption
bleeding

	ITP	HSP	Hemophilia	VWD	DIC
Bleeding Time	Prolonged	Prolonged	Normal	Prolonged	Prolonged
Platelet count	Low	Normal	Normal	Normal	Low
Platelet function	Normal	Normal	Normal	↓↓↓	Normal
clotting time	Normal	Normal	Prolonged	Prolonged	Prolonged
PTT	Normal	Normal	Prolonged	Prolonged	Prolonged
PT	Normal	Normal	Normal	Normal	Prolonged
FDP	Normal	Normal	Normal	Normal	↑↑↑ the most specific.
Specific	Anti Platelet Ab detection (IgG)	IgA C3	Factor VIII assay	VWF assay	

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IT NEVER GETS EASIER YOU JUST GET BETTER

Dr/ M. Allam MD

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